



PHARMACOLOGY

6 - 7 December 2008

Veterinary Science Conference Centre
The University of Sydney, NSW

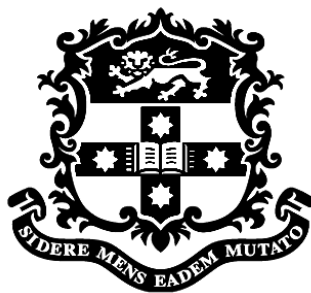
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Speaker Profiles

Dr Aitor Arteaga DVM CertSAM MRCVS

Veterinary Teaching Hospital
The University of Sydney NSW 2006
Australia

Aitor graduated from the Veterinary College in Zaragoza (Spain) in 1997. He then spent 2 years working in small animal practice in Spain before moving to the UK. After one year in general practice, Aitor completed an Internship in Davies Veterinary specialists (Hertfordshire). He was awarded a Hills residency in Small Animal Medicine at Glasgow University in 2002 and obtained the Royal College Certificate in Small Animal Medicine in 2004. Following completion of his residency, Aitor moved to Australia and has been working as Registrar in Small Animal Medicine at the Sydney University Veterinary Teaching Hospital. Aitor has completed the general examination of the ECVIM-CA diploma and is currently preparing the certifying examination.

Dr Jody Braddock BVSc (Hons) MVetClinStud FAVCSc

North Shore Veterinary Specialist Centre
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Australia

Jody graduated with first class honours from the University of Sydney and worked in private small animal practice for a number of years before returning to the University for an internship in Small Animal Medicine & Surgery and Postgraduate Diploma of Veterinary Clinical Studies. She continued at the University of Sydney as a Resident in Small Animal Medicine and completed a Masters degree (Thesis: Investigation of some alternative therapies for management of pituitary-dependent hyperadrenocorticism in the dog) and a Fellowship training program. Jody then worked at the University Veterinary Centre, Sydney as a Senior Registrar before taking up a position at the University of Sydney as Lecturer in Veterinary Medicine 2002 - 2005. She attained Fellowship of the Australian College of Veterinary Scientists in 2004 and is a registered specialist in Canine Medicine. Jody's private referral practice is now based at North Shore Veterinary Specialist Centre in Sydney and she is also continuing her clinical research - now into the long-term effects and outcomes of trilostane treatment in pituitary-dependent hyperadrenocorticism-affected dogs. Jody's clinical interests include all aspects of canine and feline medicine, especially endocrinology, gerontology, pharmacology and clinical pathology.

Dr Georgina Child BVSc DACVIM (Neurology)

Veterinary Specialist Centre, North Ryde
Veterinary Teaching Hospital, The University of Sydney
Australia

Dr Georgina Child graduated from the University of Sydney in 1980. She completed a residency in neurology and neurosurgery at University of California, Davis Veterinary Medical Teaching Hospital in 1985 and became a diplomate of the American College of Veterinary Internal Medicine (neurology) in 1987, then from 1986 to 1995 she was a research associate at Colorado State University. Georgina is a registered specialist in veterinary neurology and has worked in small animal specialist practice in Sydney since 1995, and is currently at the Small Animal Specialist Hospital, North Ryde and The University of Sydney Veterinary Teaching Hospital (Sydney).

Dr Linda Fleeman BVSc PhD MACVSc

Senior Lecturer in Small Animal Medicine
Faculty of Veterinary Science
The University of Sydney NSW 2006
Australia

Dr Linda Fleeman has recently joined the medicine team at the University of Sydney Veterinary Teaching Hospital and is an internationally renowned expert in the management of canine diabetes mellitus. She graduated from the University of Queensland; completed a clinical internship in small animal medicine at Murdoch University; followed by a clinical residency in small animal medicine at the University of Melbourne. Her PhD awarded in 2007 at the University of Queensland was on the clinical management of diabetes mellitus in dogs.

Dr Graham Swinney BVSc DVCS FACVSc

Veterinary Specialist Centre
14 Delhi Road
North Ryde NSW 2113
Australia

Graham Swinney graduated from the University of Sydney in 1987. He then took up a position at Massey University Dept of Veterinary Clinical Sciences as the Assistant Lecturer Small Animal Medicine. From there he spent 4 years at University of Queensland as the Resident in Small Animal Medicine.

In 1993 Graham returned to the University of Sydney as Registrar and subsequently Senior Registrar Small Animal Medicine gaining his FACVSc Canine Medicine.

In 1999 Graham took up the position as Clinical Assistant Professor Small Animal Internal Medicine Department of Veterinary Clinical Sciences, Washington State University.

In 2005 he returned to Sydney and is now in private practice at the Veterinary Specialist Centre in North Ryde.

He is interested in all facets of canine medicine, especially endocrinology and oncology!

Dr Adam Toyer BVSc MACVS

Batehaven Veterinary Clinic
Batehaven NSW 2536
Australia

Adam Toyer graduated from the University of Sydney with a Bachelor of Veterinary Science in 1995. After practicing in private practice for 8 or so years it became clear that whilst he knew something about veterinary science there was also a lot he didn't know. He sat and passed Australian College membership exams in Veterinary Surgery in 2007 and discovered that there were things that he knew that he knew and things he knew that he didn't know, but it was also clear there was a lot that he didn't know that he did not know! He was also fairly sure there was nothing that he didn't know that he knew. Well sort of sure. Adam has a particular interest in the management of arthritis and has presented the PGF TimeOnline Arthritis program to over 100 participants.

Adam really does believe in truth, peace, love and forgiveness. Adam hopes that his work as a vet can bring a little bit of love and joy into the lives of the animals he treats and their owners; because that is what being a vet is all about.

Dr Sanaa Zaki BVSc (Hons) MACVSc GradCertEdStud (Higher Education)

Veterinary Teaching Hospital
The University of Sydney NSW 2006
Australia

Dr Zaki graduated from the University of Sydney in 1992. She became a member (by examination) of the Australian College of Veterinary Scientists, Anaesthesia and Critical Care Chapter in 1997 and completed the Graduate Certificate in Educational Studies (Higher Education) at the University of Sydney in 2005. Since 1995 she has been teaching, conducting clinical research and providing clinical service within the Faculty of Veterinary Science at the University of Sydney. In her current position as Lecturer in Veterinary Anaesthesia she is Unit of Study coordinator for the Veterinary Anaesthesia course and Year 4 coordinator for the Bachelor of Veterinary Science degree.

In 2008, Dr Zaki was appointed Director of the University Veterinary Teaching Hospital-Sydney. She is currently also undertaking a PhD looking at "*Understanding the pain of osteoarthritis*".

Program

SATURDAY 6 DECEMBER 2008

- 9.00 – 10.00** **NSAIDs. Who Needs Them?!** **Adam Toyer**
We will look at the pharmacologic treatment of degenerative joint disease (DJD) and particularly treatment options other than NSAIDs. Disease Modifying OsteoArthritic Drugs (DMOADs), nutritional influences and the role of cortisone in treating DJD will be looked at and the evidence available for the use of each treatment assessed. No discussion would be complete however without a look at NSAIDs, the good, the bad and the plain ugly!
- 10.00 – 11.00** **Vasodilators in canine congestive heart failure** **Aitor Arteaga**
Vasodilators (with diuretics), are the cornerstone for the treatment of congestive heart failure in dogs. The traditional use of ACE inhibitors has recently been challenged with the advent of the “inodilator” pimobendan. In this lecture, we will cover mechanism of action, indications, advantages and disadvantages of these drugs. Other vasodilators used in congestive heart failure will be also discussed
- 11.00 – 11.30** *Morning Tea*
- 11.30 – 12.30** **Anticoagulant therapy** **Graham Swinney**
Anticoagulant therapy may be indicated in patients at risk of thromboembolic disease. Which diseases do we need to consider such therapy? What type of therapy should be used? Aspiring, coumarins, or heparin? If using heparin, which is best – unfractionated or low molecular weight? This presentation will address these questions and help provide a logical plan for your patients.
- 12.30 – 1.30** *Lunch*
- 1.30 – 2.30** **Which statistical lies would you like to believe?** **Adam Toyer**
Evidence Based Medicine is the new next best thing. And it has been taken up with relish universally by pharmaceutical companies. But how good is the evidence really? We will look at a number of journal articles, company flyers and advertisements and pick the eyes out to find out the information they aren't telling you as well as the stuff they are!
- 2.30 – 3.30** **Therapies for Small Animal Hypertension** **Aitor Arteaga**
Systemic hypertension is an increasingly recognised problem in small animal patients. Diagnosis and therapy of hypertension is important because sustained increased blood pressures can lead to organ damage. Therapy of hypertension includes drugs such as calcium channel blockers, ACE inhibitors, diuretics, beta blockers and angiotensin II receptor blockers. Problems associated with these therapies included refractoriness of the hypertension to drugs, poor owner compliance and adverse effects of the multiple drug regimes.
- 3.30 – 4.00** *Afternoon Tea*
- 4.00 – 5.00** **Update on gastrointestinal therapy** **Graham Swinney**
You have a patient that is vomiting, and maybe the metoclopramide has not worked. What next? There are a number of drugs that present as alternatives – which are best? Sucralfate, H2 blockers, synthetic prostaglandins, proton pump inhibitors – which should we reach for first. Find the answers to these questions, and be able to have a rational plan to determine which drug is correct in which situation.

SUNDAY 7 DECEMBER 2008

- 9.00 – 10.00 Opioid analgesics** **Sanaa Zaki**
Pharmacokinetic and pharmacodynamic differences between different opioids and how that can help determine therapy choices when managing pain in animal patients.
- 10.00 – 10.30 New drugs and techniques in small animal anaesthesia** **Sanaa Zaki**
- 10.30 – 11.00 *Morning Tea***
- 11.00 – 12.30 Management of hyperadrenocorticism in the dog** **Jody Braddock**
The key to successful management of the hyperadrenocorticoid patient is being able to select the most appropriate treatment option for a particular patient (and client!), and individualise it for that patient's needs. How and why do you choose between mitotane and trilostane? When is surgical adrenalectomy considered? Are there any other options for management of these patients? When is no treatment the best treatment? Case studies will be presented and there will be time for questions and open discussion.
- 12.30 – 1.30 *Lunch***
- 1.30 – 2.30 Treatment of non infectious inflammatory CNS disease (GME) in dogs** **Georgina Child**
Non infectious inflammatory CNS disease is the most common cause of meningoencephalomyelitis in dogs of all breeds especially toy breeds and terriers. It has a very variable prognosis. Corticosteroids remain the mainstay of therapy however other drugs may be useful in disease management and enable a reduction in corticosteroid induced side effects. The use of corticosteroids and other drugs in the management of inflammatory CNS disease will be discussed.
- 2.30 – 3.30 Insulin preparations for diabetic dogs and cats – what is new, what is still available, and how to best use them** **Linda Fleeman**
An enormous variety of insulin preparations are available and new products are continually being developed while others are withdrawn. There is currently a decline in the human diabetes market for intermediate-acting insulin products and the pre-mixed combinations of short- and intermediate-acting insulin. Unfortunately, it is these products that are most commonly used for the management of canine and feline diabetes and veterinarians must now adapt to the withdrawal of several familiar insulin preparations.
- 3.30 – 4.00 *Afternoon Tea***
- 4.00 – 5.00 Anticonvulsant therapy** **Georgina Child**
Seizures occur in up to 5% of dogs. Anticonvulsants available to treat seizure disorders in small animals will be discussed -which drugs to use and when- both in the treatment of acute seizure episodes and maintenance therapy. What you can expect from anticonvulsant therapy and the value (or lack thereof) of drug blood levels will be discussed.

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NSAIDS. Who Needs Them?!

Dr Adam Toyer

Degenerative joint disease (DJD) is the most prevalent and one of the most painful debilitating diseases in all animal species. The advent of relatively safe and effective anti-inflammatory medications has provided a dramatic improvement to the quality of life to many who suffer from DJD. Despite considerable research and investment however we still do not have a “magic bullet” treatment for DJD and many animals are either unable to use NSAIDs or have poor or limited response. Additionally there are other therapies that we can apply in addition to NSAIDs that will improve the response or reduce the doses required for good quality of life.

As this is a pharmacology focused weekend I will not go into detail about non pharmacologic or surgical therapies with the exception of weight loss. Physical therapy and regular exercise is increasingly becoming recognized as being vital to maintaining good joint function and I would strongly recommend anyone with an interest to consult with an animal physiotherapist and / or there are a number of useful reference texts available to help guide recommendations. We now also have access to surgical procedures to treat DJD with good success including total hip, knee and elbow replacement. Pharmacotherapeutic treatment is however still the mainstay of DJD treatment and maximizing the response to treatment whilst minimizing side effects is the goal of any veterinarian.

CHONDROPROTECTIVE, CHONDROPRODUCTIVE, CHONDRODESTRUCTIVE OR ANALGESIC?

When treating DJD there are 2 crucial factors to consider as to what effect the treatment has.

1. Because a majority of animals with DJD have pain then analgesia is a crucial component of therapy.
2. What long term effect on the cartilage does the treatment have?

Is it:

- a. Chondroproductive: not only stops or slows cartilage destructive processes but also enhances or improves cartilage production and repair mechanisms.
- b. Chondroprotective: stops or reduces cartilage destructive mechanisms.
- c. Chondrodestructive: accelerates cartilage destructive processes.

The ideal therapy would be both analgesic and chondroproductive. Unfortunately not all analgesics are chondroproductive or even chondroprotective and many chondroproductive therapies are slow at producing appreciable analgesia. Consequently it is usually necessary to use multiple therapies to achieve the best results in DJD cases.

WEIGHT REDUCTION

Weight reduction is the primary recommendation in all human DJD management guidelines^{1, 2}. Decreased weight leads to decreased load on joints and consequently a decrease in the forces placed on articular structures³. Recent research has focused on whether obesity in itself per se also causes DJD independent of any functional damage. Support for this theory comes from evidence that adipose tissue far from being metabolically inactive is a significant producer of various inflammatory cytokines⁴⁻⁶ including resistin, which have been shown in vitro to cause inflammation and cartilage degeneration^{7, 8}. In vivo trials have shown that calorie restriction can dramatically decrease the incidence of joint disease^{9, 10}. Recently published work has shown that a reduction in calorie intake of 25% can result in the delaying of radiograph evidence of DJD by 6 years!¹¹ The dramatic benefits of weight loss on DJD progression and pain are significant and can in many cases eliminate the need for pharmacologic analgesia.

Tips for successful weight reduction in animals

Weight reduction is a vital aspect of the clinical management of DJD in animals and yet it is one of the areas where as veterinarians we often fail to assist our clients. This is often because we feel we are not qualified or do not have enough knowledge to give our clients appropriate nutritional advice for their pets. Obesity is a medical condition whose chief aetiologic agent is food. If your clients do not get nutritional advice and nutritional products (i.e. food) for their pets from you, their vet, then they will not cure their pet's disease.

Obesity and its associated side effects can be easily and effectively CURED and prevented with nutrition. Most owners will notice dramatic improvements in quality of life for their pets within 2 weeks of starting a weight loss program. There are however a couple of tips to make sure the diet given will give the best performance in terms of weight loss:

Essential

Calorie restriction: No ifs, buts or maybes. If you do not know accurately the calorie content of the food being fed then success will be at best sporadic. I believe this to be in part one of the reasons why good quality commercial weight reduction diets are generally more successful than “home cooked” diets.

Vital:

Fibre content: Generally the higher the better. Certainly at least 15% fibre content. Anywhere up to 30% fibre content is good. Fibre provides non digestible bulk in the diet, increases satiety and decreases digestibility of other components of the diet. Dietary fibre has other effects though these are dependent on the source and type of fibre. Mostly insoluble fibre is added as it tends to cause less bowel gas production and interferes less with mineral absorption

Important:

Increased protein content: Unless protein is at least 20% and preferably 30-40% then there will be significant lean body mass lost as well as fat.

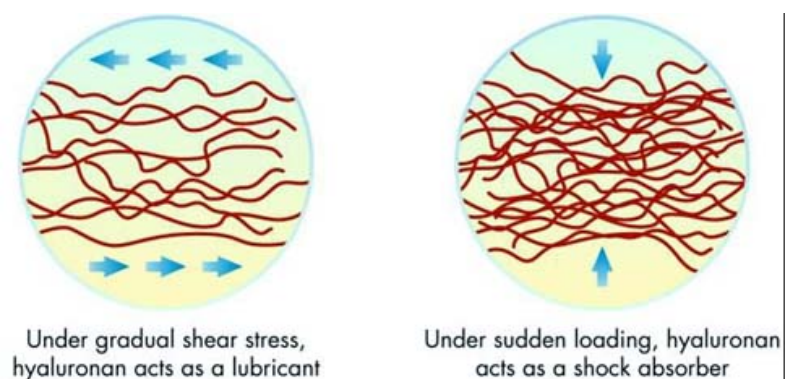
L-Carnitine: There is increasing evidence that this supplement aids weight loss by increasing fat metabolism. At this stage the evidence is positive but not conclusive. My clinical impression is that it does help when used in conjunction with above recommendations. It is found naturally in meat protein sources and is also available as a supplement.

In our clinic we have good success with Hills Canine RD food. We have also found Royal Canin Obesity to be very palatable and a good choice with small fussy dogs, and Royal Canin Weight and Osteo has the added advantage of having glucosamine and chondroitin sulphate added which may help DJD. We have generally found that pet store or supermarket “lite” foods ARE NOT suitable for weight reduction due to their generally low protein content. Indeed if you read carefully then none of these

foods claims to be able to lose weight from animals but the claim is “as an aid in preventing obesity” or along similar lines, i.e. they are for maintaining a healthy weight in an obesity prone animal.

HYALURONIC ACID

Hyaluronic acid, often also called hyaluronate, is an essential component of both cartilage matrix and joint fluid. Some years ago it was hypothesised that by supplementing joint fluid in joints affected by DJD, which are typically low in HA and have low viscosity, that the increased viscosity would help the biomechanical properties of the joint and reduce cartilage erosion. Indeed experimental models demonstrated dramatic improvements with intra articular HA that often lasted for weeks¹²⁻¹⁶. Initially it was felt that the effects were principally mechanical with the HA providing resistance to shear and compressive forces. In fact HA for use in human medicine is usually registered as a medical device, i.e. it has no biochemical or cellular effects^{17,18}. Further studies showed that the HA was cleared from the joint within seven days. Clearly there was more than a biomechanical effect on viscosity of joint fluid. Further work demonstrated that not only was intra articular HA effective in reducing DJD, but the drug appeared to have similar beneficial effects when given IV¹⁹. It is now known that HA has many and varied effects on a variety of joint tissues including reduction in inflammation, increased production of glycosaminoglycans (GAGs), and decreased production of MMPs.²⁰ Much of these effects are likely to be due to interactions of HA with the complex cellular receptor complex CD44. Current research is looking at how this occurs. Due to the long lasting nature of these effects it would seem likely that interactions with cytokines and gene expression are involved, though the exact mechanisms are yet to be determined²¹.



There are currently 2 HA products registered for use in horses in Australia; Hyonate and Enhance. As with PSGAGs, there are subtle differences in the products, most notably in the molecular weight of the HA component (high or low). Which is more effective or whether there is a difference when using IV versus intra articular is unclear at this stage. It has been suggested that larger molecular weight HA has better biomechanical properties whilst lower molecular weight HA has more cellular and biochemical effects. Hyonate is the only product registered for IV use.

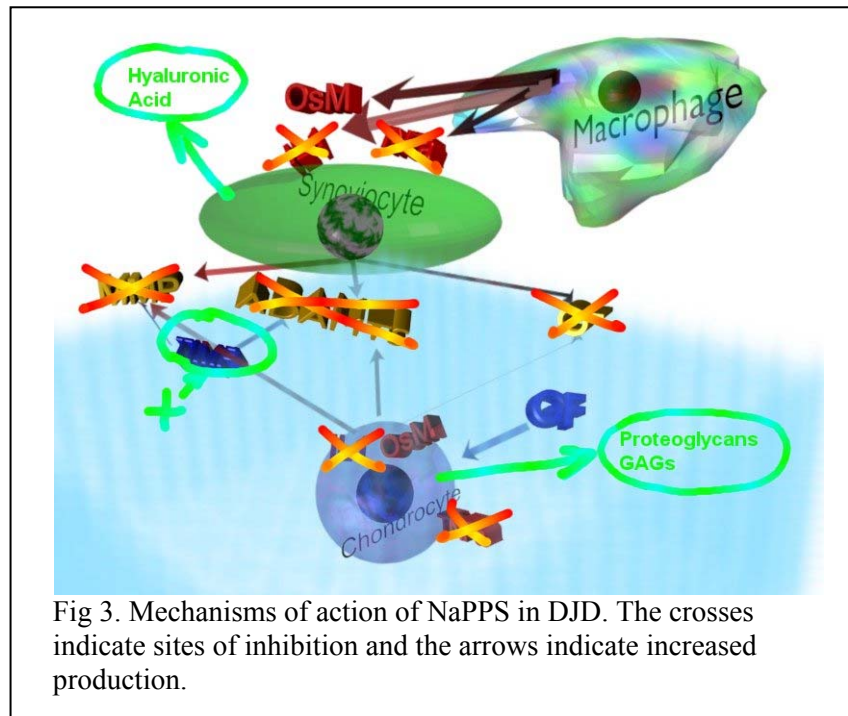
POLYSULFATED GLYCOSAMINOGLYCANS (PSGAGS)

The history of PSGAGs is interesting. Pentosan polysulphate was first used as an antithrombotic agent in humans. Work by Ghosh and others²²⁻²⁵ indicated that the drug may be beneficial in DJD. In vitro studies showed that pentosan polysulphate and PSGAG increased cartilage matrix production and decreased cartilage breakdown²⁶⁻²⁹. Intra-articular use has been associated with possible complications^{30,31} and given that systemic use was as effective as intra-articular use, most work has focused on systemic use

Differences in composition of various products and claimed benefits has been the subject of some attention. It is clear that there are demonstrable structural differences between the various products³². What is not clear is whether these differences mean that any particular product is better than any other.

These arguments aside, there is good evidence now that NaPP promotes cartilage growth and healing as well as providing significant clinical improvement in DJD³³⁻³⁶. It would appear it does this principally through the inhibition of metalloproteinases, improvement in thrombocyte function as well as the up regulation of cartilage matrix production. Certainly it would seem that NaPP is chondroprotective, and possibly even chondroproductive in the dog, and for this reason it is probably one of the most frequently used treatments for chronic DJD. Various protocols are used by veterinarians depending on their individual preference and perceived response of their patients. Typical protocols include once a week dosing for anywhere between four and six weeks, with or without follow up 'booster' doses once a month. There is no experimental support for 'booster' doses; however, intuitively it would seem that such an approach would be beneficial and certainly in our practice it would seem that dogs on 'booster' doses do better and have fewer 'relapses'. We have also used NaPP in

cats and found it to be both effective and safe, a useful combination in a species that can be somewhat of a therapeutic challenge!



TETRACYCLINES

Tetracycline and its derivatives are known to be potent inhibitors of MMPs at standard antimicrobial levels³⁷⁻³⁹. They may also inhibit NO synthesis⁴⁰. Doxycycline is a particularly effective inhibitor of MMPs and is already registered in the US as a treatment for periodontitis (which is associated with collagen breakdown by MMPs). Results with doxycycline use in the dog whilst promising have failed to show significant clinical benefits^{38, 41}. Further work on determining appropriate doses and tetracyclines with lower antimicrobial effects and greater antiinflammatory effects may yield useful treatments in the future.

CORTICOSTEROIDS

The use of corticosteroids for the treatment of DJD is controversial. Considerable debate rages over the merits and possible detrimental effects of their use in DJD. There is little

doubt that corticosteroids in either high or prolonged doses have significant catabolic effects and are generally detrimental to tissue repair. Certainly systemic corticosteroids are generally associated with far too many side effects to be a useful therapy. However, there has been a recent resurgence in interest in using intra articular corticosteroids. Intra articular corticosteroids tend to have far fewer systemic side effects with similar effectiveness to systemic use^{42,43}. Three corticosteroids in particular have received attention:

1. Betamethasone
2. Triamcinolone
3. Methylprednisolone.

Betamethasone: A medium acting potent corticosteroid that unfortunately is no longer available commercially in either human or animal formulations. Because of this there is less information regarding this medication than for triamcinolone or methylprednisolone. In vitro studies indicate at low concentrations betamethasone has no detrimental effect on proteoglycan synthesis^{44,45}. In vivo studies in the horse indicate that intra-articular betamethasone has no detrimental effect on cartilage⁴⁶. Unfortunately further work on this drug is stalled until a commercial product again becomes available with reliable quality and concentration.

Triamcinolone: Along with methylprednisolone, triamcinolone is probably the most popular long acting corticosteroid regularly used for intra articular injection. Unfortunately, good quality studies of its effects on cartilage, length of action and potency are unclear, with in vitro studies variable and often contradicting in vivo evidence. Some in vitro studies show a chondroprotective effect^{45,47,48} whilst others show no effect⁴⁹. In vivo results more consistently show either no detrimental effect or a beneficial effect in horses^{50,51}, dogs⁵²⁻⁵⁴ and humans⁵⁵⁻⁵⁸. Recent work in horses indicated a possible detrimental effect⁵⁹ but these results need to be followed up. Overall it would seem that in appropriate doses (12mg/joint in horses and 1.5-6mg/joint in dogs), triamcinolone does not exacerbate cartilage destruction and may be chondroprotective.

Methylprednisolone: Methylprednisolone acetate (MPA) is the longest acting of the corticosteroids. It has been used widely intra-articularly in horses, dogs and well as people. Unfortunately data on its effectiveness and long term effects on cartilage are scant and conflicting. In vitro studies would suggest that at certain low concentrations it is not chondrodestructive⁶⁰ although results have

been variable⁸. In vivo work in horses indicating a detrimental effect^{61,62} but studies in dogs⁶³ would indicate a chondroprotective effect. It is possible this difference is dose dependent. The dose used in the dog study was 20mg.

Despite widespread belief in both human and veterinary medicine that intra-articular corticosteroids are detrimental to cartilage healing there is little clinical evidence that this is the case⁴³. In fact it would seem in appropriate doses that intra-articular corticosteroids may be of benefit in DJD⁴³. Certainly my clinical experience is that intra-articular corticosteroids can provide long lasting relief from signs of DJD with minimal side effects or damage to the joint. In our practice we use Triamcinolone 1-3mg per joint with no more than 2 joints being treated at the same time in one animal. Note that Intraarticular Triamcinolone will cause suppression of the adrenal axis for approximately 2-3 weeks (personal data) and consequently repeat doses should be used with caution at intervals less than 1 month and concurrent use of NSAIDs should be monitored carefully for GIT side effects.

GLUCOSAMINE, CHONDROITIN SULFATE

These dietary supplements have recently become popular for arthritis treatment in humans. This is mostly due to the relative ease with which a product can be manufactured and brought to market with minimal or no licensing requirements. Unfortunately this has meant that Glucosamine and Chondroitin sulfate products are of EXTREMELY variable quality, with some little better than expensive sugar. There is evidence that regular supplementation with good quality Glucosamine sulfate has been shown in vitro and in vivo to decrease cartilage degeneration and increase cartilage production⁶⁴⁻⁶⁶. There are innumerable anecdotal and poor quality studies espousing the supposed benefits of both Glucosamine and Chondroitin sulfate in DJD. It would seem that, in patients with a high cartilage turnover (i.e. DJD), supplementation of diets low in Glucosamine and Chondroitin sulfate may be beneficial.

VITAMIN, MINERAL AND HERBAL SUPPLEMENTS

Deficiencies of various minerals and vitamins are known to cause decreased healing of various tissues. In addition, supplementation of vitamin C and zinc appears to improve bone and tendon healing. Vitamin E and selenium are both known antioxidants. Studies on super supplementation with vitamins or minerals are often poorly conducted with no controls, no blinding and a raft of complicating

factors. It would seem intuitive that, in a catabolic state (i.e. any disease), requirements for vitamins and minerals are increased; however, what the optimum levels are is anybody's guess. Caution should be exercised when super supplementing with vitamins and heavy metals as toxicity is possible, particularly with very high doses given over a long term.

Certain herbs are known to have anti-inflammatory effects. Turmeric, ginger, ginseng, ginkgo, garlic, and tea are known to contain compounds that inhibit COX or LOX enzyme systems. Many of the herbs have been used in traditional medicine systems for centuries to treat DJD and other age related diseases⁶⁷. Unfortunately, poor quality control and natural variability in the concentration of active agents means that consistent results are difficult to obtain with herbal supplements.

POLYUNSATURATED FATTY ACIDS

Structure

The term polyunsaturated fatty acids (PUFA) can refer to any fatty acid where there are at least 2 carbon double bonds in the carbon chain. Omega 3 fatty acids (ω 3FA) are PUFAs where the 3rd carbon bond from the methyl end is the first double bond whereas in Omega 6 fatty acids (ω 6FA) the first double bond is the 6th carbon bond from the methyl end. Generally in physiology we are mainly concerned with long chain PUFAs where the carbon chain is between 18 and 22 carbons.

Table 1. PUFA's of physiological significance.

Name	Formula (No. Carbons:No. Double bonds (First double bond))	Comments
Omega 3 Fatty Acids		
α-Linolenic acid (ALA)	18:3 (n-3)	Principle dietary ω 3FA
Stearidonic acid (STD)	18:4 (n-3)	
Eicosatrienoic acid (ETE)	20:3 (n-3)	COX/LOX substrate
Eicosatetraenoic acid (ETA)	20:4 (n-3)	
Eicosapentaenoic acid (EPA)	20:5 (n-3)	
Docosapentaenoic acid (DPA)	22:5 (n-3)	
Docosahexaenoic acid (DHA)	22:6 (n-3)	
Tetracosapentaenoic acid	24:5 (n-3)	
Tetracosahexaenoic acid	24:6 (n-3)	

Omega 6 Fatty acids

Linoleic acid	18:2 (n-6)	Principle dietary ω 6FA
Gamma-linolenic acid	18:3 (n-6)	
Eicosadienoic acid	20:2 (n-6)	
Dihomo-gamma-linolenic acid (DGLA)	20:3 (n-6)	COX/LOX substrate
Arachidonic acid (AA)	20:4 (n-6)	COX/LOX substrate
Docosadienoic acid	22:2 (n-6)	
Adrenic acid	22:4 (n-6)	
Docosapentaenoic acid (Osbond acid)	22:5 (n-6)	
Calendic acid	18:3 (n-6)	

Mammals are unable to synthesise a carbon double bond any closer than the 9th carbon from the methyl end of a FA. This has 2 consequences

1. All ω 3 and ω 6 FAs must be derived from the diet.
2. ω 6FAs cannot be converted to ω 3 FAs. Also on a practical level ω 3FAs are not converted to ω 6FAs.

TRANS FATTY ACIDS

The double bonds in ω FAs can occur in either a *cis* or *trans* configuration. Naturally occurring ω FAs almost always have their carbon double bonds in a *cis* configuration with the exception of some meat and milk fats from ruminants. Certain processes however including excessive heating and hydrogenation (commonly used in making margarine) can convert the double bonds to a *trans* configuration. When the double bonds are in a *trans* configuration the ω FAs are no longer able to be transformed into biologically active compounds, increase the levels of LDL ("bad") cholesterol whilst conversely decreasing the level of HDL ("good") cholesterol, inhibit the function of delta 6 desaturase as well as a variety of adverse health effects. Current recommendations from World Health Organization (WHO) and regulatory authorities in most of the developed world call for a dramatic reduction or elimination of *trans*FAs from the food chain.

EICOSANOIDS

Eicosanoids are biologically active compounds derived from 20 carbon (*Eicosa* = 20 in greek) ω FAs.

“Classic” eicosanoids

The so called “classic” eicosanoids are produced by the action of Cyclooxygenase (COX) and Lipoxygenase (LOX) enzymes on EPA, DGLA and AA. COX produces the prostanoids, prostaglandin (PG), prostacycline (PGI) and thromboxane (TX) compounds. In so doing the enzyme decouples 2 of the carbon double bonds in the substrate fatty acid to produce a particular “series” of prostanoids. Which “series” a prostanoid belongs to is designated by the number of remaining double bonds. Thus AA produces the “series 2” prostanoids such as PGF₂, PGI₂, TX₂ whilst EPA produces “series 3” prostanoids and DGLA the “series 1” prostanoids. LOX produces the Luekotriene (LT) series of compounds. Similar to COX depending on the substrate FA, LOX produces different “series” of LT’s. Unlike COX however, LOX does not uncouple any of the double carbon bonds thus AA produces LTB₄ whilst EPA produces LTB₅.

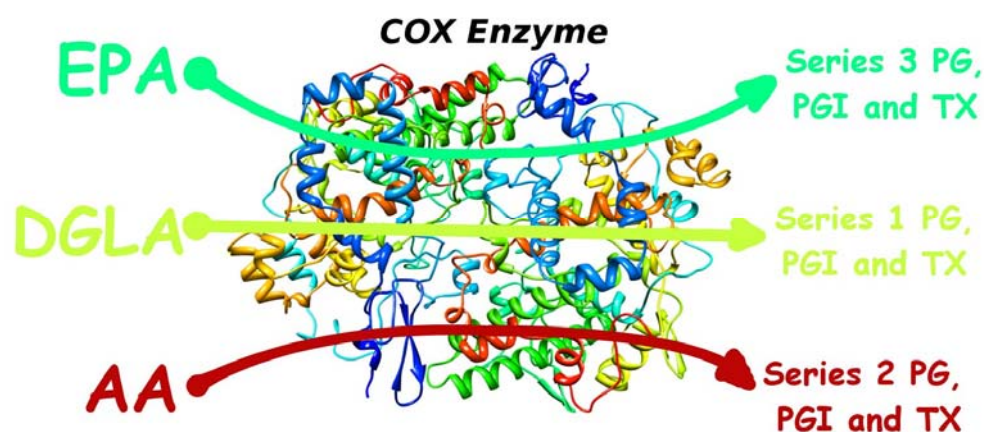


Fig. 7. Products of COX enzyme action on the 3 principal ω FAs.

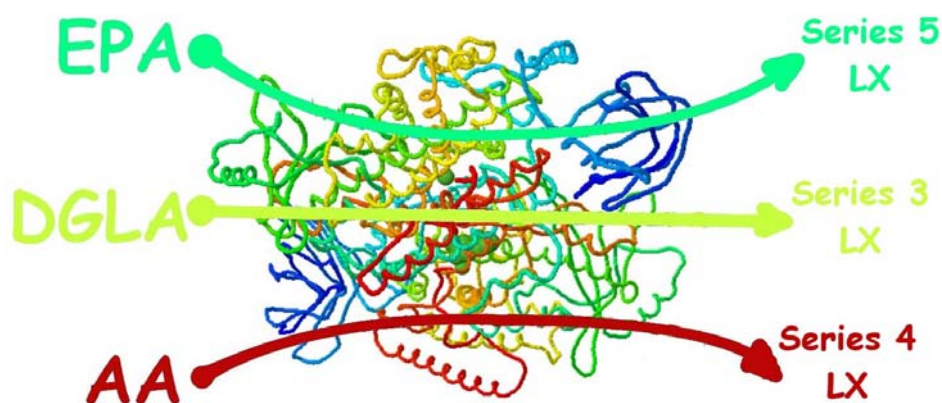


Fig. 8. Products of LOX enzyme action on the 3 principal ω FAs.

The “classic” eicosanoids have significant and often dramatic physiologic effects both locally and systemically, most notably in response to inflammatory stimuli but also in a variety of other physiologic functions as diverse as uterine contraction to adipose tissue differentiation. Whilst it is likely a gross oversimplification it can be broadly said that the AA acid derived eicosanoids (i.e. series 2 prostanoids and series 4 LTs) are strongly inflammatory whilst the EPA and DGLA derived eicosanoids (series 1 and 3 prostanoids, series 3 and 5 LTs) are markedly less inflammatory or anti-inflammatory. However each tissue produces a range of different eicosanoids, often dependent on local environment. Not only that but the same eicosanoid can have different effects on the same tissue dependent on the receptor type it binds to, e.g. PGE2 causes gastric smooth muscle relaxation when it binds to receptor EP2 whereas it causes constriction when it binds to receptor EP3. Confused?? But wait, there’s more! Enter the “novel” eicosanoids.

“Novel” eicosanoids

The novel eicosanoids are produced by non COX / LOX modification of 20 carbon ωFAs or as by products of COX / LOX eicosanoid production. They include hepxilins, resolvins, isofurans, isoprostanes, lipoxins, epi-lipoxins, epoxyeicosatrienoic acids (EETs) and endocannabinoids. Many of these compounds have only been discovered in the last 20 years and their roles are still not fully understood however it is clear that they are often AS potent as the “classic” eicosanoids and can have similar, complementary or antagonistic effects to the classic eicosanoids.

ω3 FAS AND DJD

Given the important role that many of the inflammatory eicosanoids have in DJD it would seem obvious that dietary supplementation with ω3FAs would help alleviate clinical signs of DJD. However it is only in the last 10 years that conventional scientific attention has turned to dietary effects on DJD.

Unfortunately, despite the proliferation of studies on the effects of PUFAs on various inflammatory conditions there is an enormous amount that we do not know or understand.

What we DO know:

1. Increasing the level of ω3FAs in the diet improves the clinical signs associated with DJD

- Both EPA and DHA supplementation reduce synovial inflammation, decrease nociceptor stimulation, slow cartilage degradation and may improve circulation to the subchondral bone⁶⁸⁻⁷⁰.

What we do NOT know:

- What, if any, is an “ideal” ratio of ω 6: ω 3 FAs in the diet?
- What is the “best” PUFA to supplement in the diet?
- What effect does ω 3FA supplementation have on the progression and / or development of DJD in vivo?

Our current recommendations on the use of PUFAs in the treatment of DJD are the following:

- We strongly recommend supplementation of ω 3FAs in all animals with DJD.
- We recommend the use of long chain (i.e. EPA or DHA) ω 3FAs. Substitution of ALA for LA for saturated FAs in the diet can also be of some benefit.
- We recommend ω 3FA use in dogs that are prone to development of DJD (e.g. Hip dysplasia, OCD prone dogs) though careful consideration must be given to total calorie content of the diet and ensuring the animal does not become overweight.

Various commercial diets supplemented with ω 3FA are now available (Hills JD, Royal Canin Mobility Support) and have been shown to be effective in treating clinical DJD (see websites www.hillspet.com/index.jsp and www.waltham.com). Home cooked diets with high levels of Omega 3 PUFA are possible particularly if access to fish protein sources is provided. The following table lists some useful dietary sources of Omega 3 PUFA.

Fish High in Omega 3 Fatty Acids (mostly EPA and DHA)	Omega 3 Fatty Acid Content (% of uncooked fish)
Mackerel (Atlantic)	2.3%
Albacore tuna	2.1%
Herring (Atlantic)	1.6%
Chinook salmon	1.4%
Lake trout	1.4%
Atlantic salmon	1.4%
Bluefin tuna	1.2%

Fish Oils High in Omega 3 Fatty Acids (mostly DHA)	Omega 3 Fatty Acid Content (ppm of Omega 3)
Salmon oil	4660
Menhaden oil	3620
Sardine oil	3100
Cod liver oil	2560
Herring oil	1510
Herbal or vegetable oils high in omega 3 fatty acids (mostly ALA)	
Perilla seed oil	8960
Flaxseed (Linseed) oil	7980
Walnut oil	1410
Canola oil	1300

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NOTES:

Use Of Vasodilators In Canine Congestive Heart Failure

Dr Aitor Arteaga

Congestive heart failure (CHF) is a commonly recognised syndrome in general practice. Due to different etiologies such as mitral valve myxomatous degeneration (MVMD), dilated cardiomyopathy or cardiac congenital disorders, the impaired myocardial function leads to increased venous and capillary pressures that give origin to an array of clinical signs. These clinical signs will vary depending on whether the failing side of the heart is the left, right or both sides (biventricular failure).

The pathophysiology of CHF is complex and it entails a series of intrinsic and extrinsic compensatory mechanisms. The intrinsic compensatory mechanism is the ability of the myocardium to respond to pressure or/ and volume overload with hypertrophy, dilation or a combination of both. The extrinsic mechanisms include a composite of neuro-hormonal mechanisms, namely the sympathetic nervous system and the rennin-angiotensin-aldosterone system. The aims of these mechanisms are to maintain blood volume, central venous pressure, venous return to the heart and cardiac output. The initial consequences of the neuro-hormonal stimulation are positive and result in compensation of the haemodynamic abnormalities. However, as cardiac disease progresses, these mechanisms become counterproductive.

Medical therapy of CHF is aimed to target the following imbalances:

1. Control of extracellular fluid (reduce oedema and effusion)
2. Promote tissue perfusion (increase cardiac output and reduce vascular resistance)
3. Regulation of the neurohormonal imbalances
4. Correction of the heart rate and rhythm

The use of diuretics to reduce oedema and effusion formation fluid has been long recognized as an effective therapeutic approach. Diuretic are the most efficacious drugs used in the therapy of CHF.

In dogs with heart failure, both veins and arterioles are constricted as a result of the stimulation of the renin-angiotensin-aldosterone system. The aim is to maintain the blood volume to increase the preload and the cardiac output and to preserve the systemic blood pressure. As mentioned earlier, these compensatory mechanisms may become counterproductive, leading to:

1. An overwhelming volume expansion which leads to excessive preload and oedema or/ an effusion formation.
2. Increased blood flow resistance (excessive afterload) leading to decreased cardiac output and increased energy consumption.

Therefore, one of the corner-stones of the therapy in CHF is the use of vasodilators to relax the arterial and venous smooth muscles. The aim is to reduce the afterload (the resistance to ejection from the ventricles) promoting the forward flow and the preload (the blood volume reaching the heart by increasing the total venous capacity). The main mechanisms involved include reduction of the intracellular calcium and dephosphorilation of myosin. The net effect is the elimination of the vascular muscle contraction dependant on the increase of intracellular calcium and the phosphorylation of the myosin protein resulting in relaxation of the vascular smooth muscle or vasodilation.

The main side effect of any vasodilatory drug is hypotension. These effects are more prominent when given concurrently diuretics and/or when more than one vasodilator is used. Monitoring the blood pressure in these patients is necessary. The aim is a mean arterial pressure of over 70-80 mm of Hg (below 65 mm of Hg there are signs of hypotension such as weakness and lethargy).

We can classify the different vasodilators depending on the site of action:

- **Venodilators**

1. Nitroglycerine

- **Arteriodilators**

1. Amlodipine
2. Hydralazine
3. PDE V inhibitors

- **Mixed vasodilators**

1. ACE inhibitors
2. Pimobendan
3. Nitroprusside
4. Prazosin
5. Angiotensin II antagonists

NITROGLYCERINE

Nitroglycerine or glyceryl trinitrate is a nitric oxide donor that acts by reacting with sulphhydryl groups of the vascular smooth muscle cell. This leads to activation of the enzyme guanylate cyclase that forms cGMP from GTP leading to efflux of intracellular calcium and stimulation of light chain myosin phosphatase resulting in smooth muscle relaxation. It acts mainly as a venodilator (arteriodilator only on high doses intravenously) in dogs and cats although there are no clinical studies available. It has been advocated for acute failure situation (such as acute pulmonary oedema) but efficacy is unproven (effect could be attributed to the high doses of frusemide given concomitantly). Tolerance to the effect of this drug may occur after 24 hours due to exhaustion of vascular endothelial reserves of sulphhydryl groups impairing the transformation of nitroglycerine into nitric oxide. This is avoided by administering this drug for a maximum of 3 days and rest 1-2 days to repletion of sulphhydryl groups.

It is available in cream (not in Australia), spray and patches. The cream has to be applied with gloves (due to hypotension leading to headache, dizziness). Doses described in the literature for dogs and cats are empirical.

2% cream: $\frac{1}{2}$ to 2 "every 4-6 hours for dogs and $\frac{1}{8}$ to $\frac{1}{4}$ "every 4-6 hours for cats (although percutaneous absorption may be very poor).

If patches: 0.1 mg/hr patches for small dog and 0.2 mg/hr patches for larger dogs

HYDRALAZINE

Hydralazine is a direct acting smooth muscle relaxant of the arteries and arterioles. It has no effect on venous muscle tone. The mechanism of action is unclear but it likely increases the intracellular concentration of prostacyclins in the smooth muscle of the arterioles, leading to the dephosphorylation of the myosin proteins. Due to the resulting reduction in vascular resistance, it causes “baroreceptor reflex” (sympathetic stimulation leading to increased contractility and cardiac output). It may also stimulate stimulation of the rennin-angiotensin-aldosterone system (when used in hypertension is normally administered with a beta-blocker). However in dogs with CHF both the sympathetic system and the rennin-angiotensin-aldosterone system are already activated and these effects are not commonly seen. Its use is restricted to cases that are refractory to ACE inhibitors and those with acute CHF (when nitroprusside infusion is not possible). It is a very potent drug (reduction of the systemic vascular resistance of up to 40%); therefore most common side effect is hypotension particularly when used with other vasodilators such as ACE inhibitors. Blood pressure should be monitored (reduction of 15-30 mm of Hg suggest effective action). Effect is noted within one hour and peaks 3 hours following administration. Net duration of effect is 12 hours. Other common side effects (20-30% of cases) include gastrointestinal effects such as vomiting and diarrhoea. These effects can be managed by reduction of the dose. If signs are persistent other arteriodilator such as amlodipine may be used instead. Recommended doses vary between 0.5-2 mg/kg PO BID. Dose must be titrated “slowly” while measuring the blood pressure.

AMLODIPINE

Amlodipine is an arteriolar vasodilator. It is a member of the calcium channel blocker drug family. It has a long half-life in dog (up to 30 hrs) and a bioavailability of 88%. It reaches peak effect after 2-3 days. It has similar use in refractory heart failure and in severe mitral valve regurgitation reducing oedema and improving cardiac output to hydralazine but it maybe less likely to cause side effects such as reflex tachycardia. One study in dogs with MMVD but not heart failure showed 10% reduction of BP and reduction of regurgitant fraction with no change in heart rate and no adverse effects. Another study showed activation of the rennin angiotensin system in normal beagle dogs but this effect was partially blunted with enalapril. The combination of both showed a trend towards increased HR and azotaemia albeit both were mild. It has been shown to prolongs survival in people with DCM and also improves clinical signs and exercise intolerance in people with heart failure.

Amlodipine may be costly in large dogs. The recommended dose varies from 0.05 mg/kg BID to 0.2 mg/kg. Starting dose should be 0.05 mg/kg and it may be increased while monitoring blood pressure.

NITROPRUSSIDE

Nitroprusside is a mixed vasodilator that acts mainly as a nitric oxide donor. It is available as an intravenous drug. It is rarely used in veterinary practice due to the need of close blood pressure monitoring (should be maintained over 70-80 mm of Hg) and intravenous administration but it is useful in acute and severe CHF, particularly in those patients that are showing diuretic resistance. Weaning the patient of the medication may be difficult due to rebound vasoconstriction. Long acting drugs such as hydralazine or amlodipine should be administered while the dose of nitroprusside is tapered. Doses between 2-10 mcg/ kg/ min are recommended. Side effects include hypotension and cyanide toxicity (brick red mucous membranes due to hyperoxemia, dyspnoea, lactic acidosis) at doses over 10 mg/kg. Nitroprusside needs to be protected from light, heat and moisture.

PRAZOSIN

Prazosin is an α_1 adrenergic-receptor (responsible for vasoconstrictive effect of the norepinephrine) blocking agent that causes both arteriolar and venous dilation. It may have some use in dogs with renal hypertension. Also used in patients with micturition problems.

Side effects include hypotension (mainly associated with the first dose), vomiting, diarrhoea, anorexia and syncope.

Dose: 1 mg Q8 hrs for dogs < 15 Kg and 2 mg Q8 hrs for dogs >15 Kg. May be modified depending on response and blood pressure.

PDE V INHIBITORS

These drugs are potent and selective inhibitors of PDE 5. This enzyme degrades cGMP. PDE 5 inhibitors bind to this enzyme, increasing the cGMP. This leads to dephosphorylation of the myosin fibrils and vasodilation. PDE 5 receptors are present in the arterial smooth muscle of the lungs. Thus their use in small animals is restricted to those patients suffering of pulmonary hypertension.

In dogs, they appear to be well tolerated and improve pulmonary arterial pressures. Drugs of this group include sildenafil and tadalafil.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

These drugs block the action of angiotensin II at the level of the receptors. This leads to reduction of aldosterone, ADH secretion and vasodilation. Their main use is as anti-hypertensive in those patients that do not tolerate (cough) or cannot have ACE inhibitors. They are also used in human patients with CHF. They show similar effects and potency to ACE inhibitors. There are no controlled studies of these drugs in dogs with CHF. Side effects include hypotension, dizziness, hypokalaemia, diarrhoea. Drugs of this group include Losartan, valsartan, olmesartan and irbesartan.

The other two vasodilators are ACE inhibitors and the Phosphodiesterase III & V inhibitor and calcium sensitizer Pimobendan. These are the main focus of this lecture. They also possess other actions that makes them useful in the setting of CHF.

ACE INHIBITORS

One of the most studied group of drugs both in human and veterinary medicine. Angiotensin converting enzyme (ACE) inhibitors bind to ACE at the point where angiotensin I is arrested its conversion into angiotensin II (AII). The effects of this decrease in AII concentration are multiple:

1. Vasodilation due to decrease in AII (vasoconstrictor) and reduced degradation of bradykinin (vasodilators).
2. Reduced production of aldosterone (reduced Na and water retention/ myocardial remodeling)
3. Reduced ADH secretion (reduced water retention).
4. Effects in sympathetic nervous system.

They are mixed (or balanced) vasodilators leading to both a decrease in preload and afterload. However they also have an important role in regulation of the neuro-hormonal imbalances in patients with CHF. ACE inhibitors have been shown to prolong life and improve quality of life in humans with heart failure (months). They have also been proven to delay onset of heart failure in asymptomatic humans with heart disease.

Several studies have shown their efficacy and safety in dogs with CHF and in dogs ACE inhibitors are with diuretics part of standard therapy. However, they have little use in acute heart failure. Adverse effects such as hypotension are rare. However, despite evidence of renoprotective effect in patients with chronic administration of ACE inhibitors, functional azotaemia (due to preferential efferent arteriolar vasodilation leading to decrease in GFR) can still occur. Predisposing factors include dehydration and hyponatraemia. Assessing renal function after initiation of ACE inhibitors is recommended. There are several ACE inhibitors available, including captopril, enalapril, benazepril, ramipril and imidapril. The main differences within these drugs lay in the duration of action and so dose and frequency varies depending on the drug.

PIMOBENDAN

Pimobendan is the latest drug to become part of the routine therapy of dogs with CHF due to DCM or MDMVD. Pimobendan is a benzimidazole pyridazinone derivate that acts as inodilator. It causes mixed vasodilation (via PDE III and V inhibition) and has positive inotropic effect (both via PDE III and also via calcium sensitisation). This leads to reduction of afterload and preload and increased contractility. It maybe used in acute heart failure as it is rapidly absorbed (1-2 hours). It may also be useful in patients with pulmonary hypertension (PDE V inhibition).

Adverse side effects are rare and include progression of valvular dysfunction and ventricular hypertrophy. Arrhythmias are a side effect observed in humans treated with PDE III inhibitors. However, arrhythmias have not been commonly detected in several trials in dogs. Different studies were performed in humans with heart failure treated with pimobendan leading to conflicting results. It was removed from the market due to a trend in increase in mortality in one study.

Dose for dogs varies from 0.25-0.3 mg/kg PO BID one hour before food.

In the last years pharmaceutical companies have launched aggressive campaigns promoting the use of different vasodilators for the therapy of canine CHF. To attempt to cast some light into this issue, in the present lecture we will discuss the findings of some of the most relevant articles on the use of ACE inhibitors and pimobendan in the recent veterinary scientific literature.

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NOTES:

Which Statistical Lies Would You Like To Believe??

Dr Adam Toyer

WHAT IS EBVM?

There has recently been much made of the importance of “Evidence Based Veterinary Medicine” (EBVM) and its use in veterinary practice. This has followed a similar trend in human medicine which questioned the effectiveness of many popular treatment methods which when analysed systematically and closely proved to be of little or no benefit. This then led to an effort to establish a method for selecting the best and most effective treatment for a patient based on available evidence. “Evidence Based Medicine” was born.

The Centre for Evidence Based Medicine (www.cebm.net) does not give a hard definition for EBM however it can be summarized as:

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

The above summary also describes well the concept of EBVM where the patient becomes the animal under the veterinarians care.

It is worth reading the above summary CAREFULLY. In particular I would encourage readers to note the use of the term “best” when qualifying which evidence should be used. EBVM is not about counting up who has the most positive published studies versus negative studies but involves an assessment of the quality of the available evidence and selection of the “best” quality studies to provide the evidence for decision making.

WHAT EVIDENCE IS “BEST”?

Clearly if we are trying to establish a systematic and repeatable method for determining the best treatment options for a patient

then we cannot rely on an arbitrary assessment by some author or another of what qualifies as a “good” or “best “ quality evidence. Thus we need a framework for ranking the quality of evidence. There are a number of frameworks available for ranking evidence based on the type of study that provided the evidence and some can become somewhat bewildering with subcategories etc.

Almost all publications can be broken down into 3 basic categories:

Research Synthesis: Meta Analysis and Systematic reviews.

Primary research: Randomised Controlled Trials, Cross Over, Cohort, Case control studies, (Cross sectional surveys).

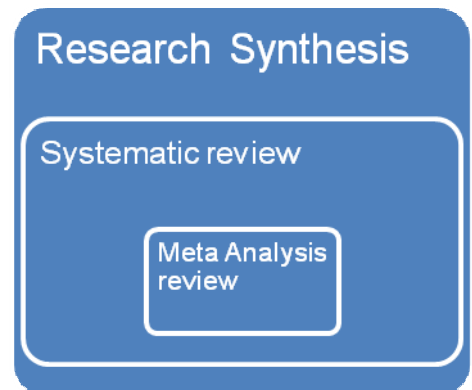
Uncontrolled and non clinical information: Case series, Case studies, in vitro research, studies in other species, expert opinion, textbook chapters.

RESEARCH SYNTHESIS

The Systematic review is basically a study of available evidence. As such there are certain essential elements. Firstly there must be a clear method that describes exactly how the evidence was collected so that if someone were to repeat the method they would get the same results.

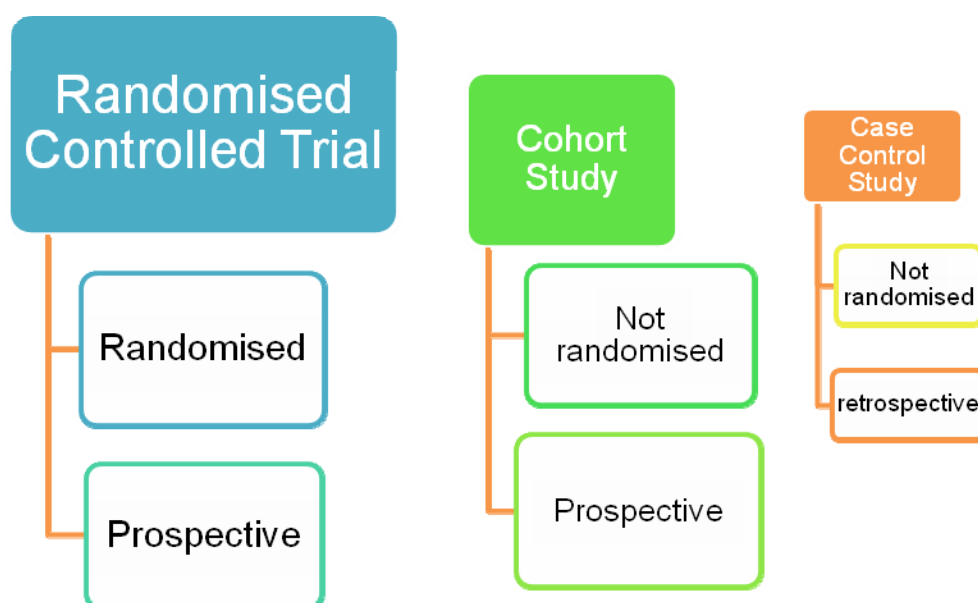
Secondly the results must be presented truly so that when the review is read the conclusions reached in the discussion can be verified from the results. A Meta Analysis is a very specific type of systematic review where the methods from the studies found are similar enough that they can be pooled and analysed as if they were one study with the concomitant increase in the statistical power of the results.

Systematic reviews and Meta Analysis provide the best quality evidence for a particular clinical question.



PRIMARY RESEARCH

Primary research can be classified as studies that compare 2 or more groups of animals' response to treatment / disease / diagnostic test etc. One or two of the groups acts as a known control where the treatment applied is known to be either non beneficial (i.e. placebo) or beneficial (positive control) and the remaining groups are compared to the known group/s to assess effectiveness. The quality of a primary research studies findings is improved by blinding assessors and / treatment appliers to the treatment used. Prospective studies provide better quality evidence than retrospective studies and randomized studies provide better evidence than non randomized studies.



The cross over study is a specialized type of study where animals act as their own controls and after a period of time are switched from treatment to control group. This is only really feasible when studying chronic diseases. The Cross sectional survey is another specialized type of primary study that takes a “snapshot” at a particular moment in time and is useful principally as a study to determine disease prevalence.

Primary studies provide the foundational clinical information for providing clinical recommendations. Individual primary studies on their own do not provide conclusive evidence of the usefulness of a particular treatment, rather they supply the building blocks for constructing the EBVM picture.

UNCONTROLLED AND NON CLINICAL INFORMATION

This group of published information forms probably the largest of all published information. Unfortunately it's usefulness is limited due to the highly variable quality and difficulty in verifying the information presented. Text book chapters are little more than referenced expert opinions and consequently subject to considerable bias. Unreferenced expert opinions should be viewed with a great deal of caution. Case studies, case series, invitro research and research from non target species **can not** be used to construct answers to clinical questions. Such information can however be useful in formulating hypothesis for testing with primary research studies or for elucidating and researching unusual or unexpected clinical findings.

COMMON OR INHERENT FAULTS OF PUBLISHED STUDIES

Just because an articles title says it is a “systematic review” this does not automatically confer infallibility of the articles findings. A poorly conducted systematic review with an arbitrary method of study selection is little better than a souped up expert opinion! Careful attention needs to be paid to all parts of the study, including the method and results. Important questions one should be asking include:

- A. Are the aims of the study clear and are the underlying assumptions of the study valid?
- B. Are the methods appropriate? In particular has there been adequate randomization, are selection criteria clear and unambiguous, are assessment methods objective or subjective, is the model a valid model of clinical occurrence?
- C. Have the results been appropriately analysed? Have appropriate statistical tests been used. Are there mathematical errors in the results analysis?
- D. Are the conclusions reached in the discussion justifiable from the data presented?

As an example let's look at the following article published in Veterinary Therapeutics in 2006.

Vet Ther. 2006 Summer;7(2):119-26.

Clinical Effectiveness and Safety of a New NSAID, Firocoxib: A 1,000 Dog Study*

William G. Ryan, Katherine Moldave, Doug Carithers

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CLINICAL RELEVANCE

For the Previcox (firocoxib, Merial) Experience Trial, practicing veterinarians across the United States were asked to enroll dogs diagnosed with osteoarthritis. At an initial visit, owners of dogs deemed suitable for NSAID therapy were given Previcox and instructed to maintain a daily diary and to return 10 and 40 days after treatment began. Approximately 86% of 1,002 enrolled dogs completed the study. The withdrawal rate associated with gastrointestinal side effects was low (2.9% of dogs), and no serious drug-related adverse events were reported. Investigators and owners rated 93% and 91% of dogs, respectively, as improved, and 86% of owners rated their dogs “happier” or “more active” after treatment with firocoxib. The improvements observed following initiation of firocoxib therapy were independent of gender, breed, starting body weight, age, and prior NSAID use. These results support previous findings that firocoxib is well tolerated and effective when used under field conditions.

*Funding for this study was provided by Merial Limited, Duluth, Georgia.

INTRODUCTION

Previcox (firocoxib, Merial) is a cyclooxygenase (COX)-2-selective/COX-1-sparing NSAID - developed specifically for veterinary use following demonstration in canine whole blood assays that it is approximately 380-fold selective for COX-2 over COX-1.¹ While these COX enzymes are believed to play a role in the health and repair of the gastrointestinal mucosa, the failure of nonselective NSAIDs to spare COX-1 has been indicted as the major factor contributing to the adverse effects associated with their use.² Serum levels of firocoxib necessary to provide peak inhibition of COX-2 have little impact (0%–3%) on COX-1 activity, and field trials have demonstrated that firocoxib is associated with fewer side effects and improved efficacy over less COX-1-sparing NSAIDs against which it has been compared, including carprofen and etodolac.^{3,4}

The objective of the Previcox Experience Trial (PET) was to familiarize veterinarians with the clinical utility of Previcox for the relief of canine osteoarthritis (OA)-related inflammation and pain. The clinical acceptability would be demonstrated by the assessments of participating veterinarians (investigators) and dog owners (owners) of the acceptability and tolerability of firocoxib and the improvement in lameness that it produced. Although the study was undertaken to allow veterinary practitioners and specialists to gain experience with firocoxib, it also allowed the expansion of an already extensive clinical performance database compiled during registration studies.

MATERIALS AND METHODS

Investigator Qualification and Patient Recruitment

Practicing veterinarians were invited to participate in a live Webcast or to review a Webcast

archive that provided an overview of clinical use of NSAIDs in dogs for treatment of OA, a presentation on the newly registered firocoxib, and an outline of the trial protocol. Veterinarians who chose to enroll as investigators were assigned a site number, and identifying information was entered in the PET database.

A trial binder containing the protocol and relevant study forms was then shipped by the Trial Data Coordinator to the participating practices. Firocoxib to be used in the study was also shipped directly to the clinics.

Study Enrollment

Exclusion criteria were provided by Merial, but the decision as to whether a given patient was enrolled in the PET was the responsibility of each investigator, based on his or her clinical assessment of the needs of each patient. Investigators were informed of exclusion criteria, which included recent elective surgery; pregnancy or lactation; concomitant conditions such as gastrointestinal, renal, or hepatic disease; or any evidence of systemic disease or infectious arthritis. Owners of dogs that were receiving an NSAID or corticosteroid at the time of the enrollment visit were asked to observe a washout period thought to be sufficient for clearance before initiating treatment with firocoxib ([Table 1](#)).

The enrollment objective was 10 dogs/site at a minimum of 100 sites. Enrollment occurred from the date of the Webcast on April 21, 2005, through October 8, 2005.

Study Design

The protocol, prepared in consultation with an advisory committee of American College of Veterinary Surgeons–boarded surgeons, required three scheduled office visits:

- Initial enrollment visit (day –3 to day –1)
- A visit 7 to 10 days after initiation of treatment (~day 10 post–treatment initiation)
- Final visit or study end (~day 40 post–treatment initiation)

All candidate dogs enrolled in the trial were to have been diagnosed with OA by an investigator as a prerequisite for inclusion in the trial. Whether such diagnosis included radiology was left to the discretion of each investigator. At the initial visit (day –3 to day –1), the investigator determined that a given patient might be a candidate for the PET (i.e., the dog had a preexisting diagnosis of OA), conducted a physical examination, obtained the required blood samples for comprehensive serum chemistry and hematology analyses, completed a Case Details (Enrollment) Form, dispensed a 10-day supply of firocoxib, and handed out the Owner Observation Form (i.e., owner diary). After a review of the laboratory results, the investigator determined a patient’s eligibility for study participation and contacted the owner accordingly.

For the ~day 10 assessment, the patient was returned to the investigator for a physical examination and a repeat of the laboratory work. The owner also brought his or her initial Owner Observation Form for review. The investigator completed a ~day 10 evaluation, which consisted of one question answered separately by the owner and the investigator: “How would you describe the dog’s lameness since initial visit?”

Investigators and owners chose from the following:

- Greatly improved
- Moderately improved
- Mildly improved
- Not improved
- Worse

The procedure was similar for the final visit, at which point the investigator reviewed and collected the Owner Observation Form. Owners were asked questions about palatability (whether the dog readily accepted the tablet), convenience (palatability and ease of administration if the dog did not accept the tablet readily), and their impression of the dog's quality of life. After the final visit of the last dog enrolled at each clinic, investigators compiled their PET forms in the PET Binder issued to each investigator before the start of the study.

RESULTS

Enrollment

Investigators at 106 sites in 36 states enrolled 1,002 dogs in the trial. Of these, 954 dogs returned for the ~day 10 evaluation; evaluations for 864 dogs were submitted at the final (~day 40) evaluation. Dogs enrolled slightly favored females over males; ages ranged from 6 months to 16 years, and weights ranged from 4 to 199 lb (1.8–90.5 kg). Mixed-breed dogs represented the largest enrollment category, followed by Labrador retrievers, golden retrievers, and German shepherds. OA was diagnosed in a single joint for approximately half of the enrolled dogs; multiple joint involvement was diagnosed in the remaining animals.

Of the 1,002 dogs enrolled in the study, 458 (46%) were reported as having been treated previously with at least one NSAID; 544 (54%) were reported by investigators as having no history of NSAID treatment. Approximately 23% had a history of treatment with carprofen, 12% with deracoxib, and 11% with meloxicam at some point before initiation of treatment with firocoxib.

NSAIDs used within the week (7 days) before initiation of treatment with firocoxib included aspirin, carprofen, deracoxib, etodolac, meloxicam, piroxicam, and tepoxalin. On the Case Details Forms, investigators identified 195 dogs (19.5% of enrollees) as having been treated with carprofen, deracoxib, or meloxicam within the week before treatment with firocoxib.

Trial Noncompleters, Blood Analysis Results, and Potential Adverse Events

From a preliminary screening of 1,135 dogs, 1,002 were enrolled in the study. In general, investigators did not convey their reasons for disqualifying dogs after the preliminary blood screening. However, elimination may be attributed to factors such as blood test results that either were deemed unsatisfactory by the veterinarian or indicated the presence of disease precluding treatment with an NSAID, owner schedules, and other owner-related considerations.

Of the 1,002 dogs enrolled in the study, 135 (13.5%) were withdrawn ([Table 2](#)), including 11 reported to have died or been euthanized for reasons not linked to treatment ([Table 3](#)). Of the dogs that were withdrawn, the most common single reasons were vomiting (1.9% of the total dogs enrolled) and elevations in blood chemistry (most commonly blood urea nitrogen) that were of concern to the investigator. Although additional events of vomiting were recorded in the owner diaries, these episodes were transient and mild and generally were not attributed to

treatment. None of the deaths that occurred during the trial were attributable to the types of gastrointestinal, renal, or hepatic events that typically have been associated with NSAID use.

Laboratory Results

Despite the recommended guidelines to exclude dogs with signs of renal or liver disease, 7% of dogs enrolled in the trial had elevated blood urea nitrogen (BUN) values and 26% had elevated alanine transaminase values. Nonetheless, mean BUN levels remained within the normal range throughout the study. For any dogs with elevated BUN and creatinine levels or increased alanine transaminase or aspartate aminotransferase levels combined with an increased alkaline phosphatase level, owner records were reviewed in detail to determine if such blood chemistry changes were associated with any clinical signs of disease. Total bilirubin results were also assessed in dogs that had elevated liver enzymes, and all were found to be unremarkable.

Blood test results were reviewed to determine if any elevations in blood values could be temporally associated with gastrointestinal events described in an owner's diary but not necessarily reported to the investigator. No direct links were noted. Even though some owners observed instances of vomiting and/or diarrhea in their dogs and noted them on the Owner Observation Form, generally neither the owner nor the investigator considered these episodes to be a concern or a reason to discontinue use of firocoxib.

Efficacy Results

Similar improvements in OA were observed in male and female dogs and in dogs of different breeds, weights, and ages evaluated at each assessment. There was also essentially no difference in rate and degree of improvement between dogs with a history of NSAID use and those without such a history.

Investigator and Owner Evaluations

At the first post-enrollment visit (~day 10; $n = 954$), investigators rated 88.2% of dogs as improved (mildly to greatly improved) and 11.8% as unimproved ([Figure 1](#)). Owners rated 87.4% of animals as improved and 12.6% as unimproved ([Figure 2](#)). At study end (~day 40; $n = 864^a$), investigators rated 92.8% of dogs as improved whereas owners rated 90.8% of animals as improved. Both the investigator and owner assessments demonstrate that improvement occurred throughout the course of the study, with more dogs showing overall improvement and more dogs showing great improvement at ~day 40 than at ~day 10.

Veterinary evaluation of those dogs demonstrating the higher degrees of improvement ("moderately improved" and "greatly improved") increased from 57.3% at ~day 10 to 75.8% by the end of the trial (~day 40). Owner evaluations reflected the same trend throughout the trial, as dogs demonstrating great or moderate improvement climbed from 60.2% at the intermediate visit (~day 10) to 75.2% by the end of the trial (~day 40).

Similar improvements in signs of OA were observed in male and female dogs and in dogs of different breeds, weights, and ages. Additionally, when the participating animals were segregated into these subsets, similar patterns and tendencies of improvement were seen regardless of the category or breakdown. For example, results for each subgroup at the ~day 40 investigator analysis for each weight band ([Figure 3](#)) were very similar to the ~day 40 investigator results in [Figure 1](#).

The reported improvements in dogs with a history of receiving carprofen, meloxicam, or deracoxib in the week before enrollment did not appear to differ from those that had no such history (Figure 4).

Among owners responding to questions on palatability and convenience of administration of the firocoxib formulation, just over 90% rated the firocoxib flavored tablet as convenient to administer and 79% reported that their dogs found firocoxib palatable. Among owners responding to each question on their perception of their dog's attitude ("Is your dog more active since starting treatment?" "Is your dog happier since starting treatment?"), 86% reported that the dog was more active and 86% that the dog was happier.

DISCUSSION

With more than 1,000 dogs enrolled and more than 100 investigators involved, the Previcox Experience Trial is the largest single canine NSAID postmarketing study ever undertaken. The results substantiate earlier studies showing favorable effectiveness, tolerability, and overall safety of firocoxib. The absence of a control group and of investigator and owner blinding and the related absence of a valid statistical analysis precludes definitive conclusions on the overall efficacy of firocoxib; however, this national trial (1) addresses the need for more information on newly approved products, (2) generates in-clinic experience that normally builds over an extended period, and (3) provides systematic records of important aspects of product performance. Large-scale postregistration clinical studies are well accepted and well established in human medicine, and similarly, this trial should be beneficial for veterinarians.

The PET demonstrated that dogs prescribed firocoxib for treatment of OA showed substantial improvement within 10 days of initiation of treatment and that the pattern of improvement continued over time. A larger percentage of dogs showed improvement at the end of the trial (~day 40) than at the intermediate visit (i.e., 1 week to 10 days after treatment began). Whereas studies of extended duration are desirable to confirm the continuing efficacy and safety of firocoxib (or any canine NSAID) over long-term use, the results of this study suggest a cumulative benefit that becomes more apparent with continued therapy. Possible reasons for such continued improvement might include a return of muscle tone associated with increased use of the affected limb or a progressive reduction in inflammation around the affected joint.

More than 90% of dogs were rated as improved (mildly, moderately, and greatly) by investigators and owners, and rating patterns over the course of the study were similar for investigators and owners. Because the clinic and home environments are so dissimilar and would be expected to affect animal disposition, this consistency is particularly interesting.

Improvement was seen regardless of age, gender, breed, body weight, or prior NSAID use. This study suggests that for dogs receiving a different NSAID, there can be clinical benefits associated with switching to firocoxib. Moreover, owner responses indicating that in 86% of cases their dogs were "happier" or "more active" suggest the benefit of treatment with firocoxib on quality of life.

The low rate of gastrointestinal events sufficiently severe to withdraw a dog from the study matches observations reported in earlier studies with firocoxib.⁵ Consistent with expectations, many of the dogs entering this study were advanced in years and thus more susceptible to concomitant conditions, including exposure to other medications (with or without the

investigator's knowledge) and to NSAID toxicities. In fact, some dogs were presented with underlying illnesses in addition to OA, and approximately one-third of enrolled dogs had elevations beyond the normal range in at least one blood chemistry measurement before starting the trial. However, this may be attributed to the "real-life" trade-off between the risks of exacerbating an existing pathology by repeated NSAID treatment and the benefit of quality-of-life improvement gained by use of the NSAID.

Despite the enrollment of dogs with conditions that would be expected to lead to increased susceptibility to NSAID side effects, overall results of clinical observations and blood chemistry are consistent with earlier reports of overall safety and acceptability of firocoxib. Nonetheless, as would be expected for any NSAID used in the population of dogs enrolled in this study, there were some elevations in BUN, creatinine, and liver enzyme levels (albeit generally without any outward clinical sign) in a small number of dogs during the treatment period. These findings confirm the ongoing need for monitoring of blood chemistry and clinical presentation of any dog undergoing NSAID therapy.

For many practices, participation in a clinical trial was a new challenge that presented organizational hurdles related to coordinating owners' return visits with investigators' in-clinic schedule. An impression that arose from telephone discussions with investigators and from other contacts with PET sites is that the clinics that adapted best to the trial routine were those with a capable technician who maintained the trial organization.

Entries in owner diaries ranged from cursory to exhaustive and provide a potentially useful view of how owners approach evaluating and balancing the health and quality of life of their dogs. Some observations focused on behaviors, others on level and type of activity, and still others on patterns related to appetite, elimination, and other gastrointestinal factors. In some instances, experiences and expectations specifically in terms of NSAIDs were fairly clear. For example, some owners offered comparisons of firocoxib to other NSAIDs, and some owners appeared to be anticipating the appearance of gastrointestinal side effects. Overall, more than 90% of dogs were rated as improved (mildly, moderately, or greatly), and rating patterns over the course of the study were similar for investigators and owners.

SUMMARY

One hundred six veterinary practices in 36 states enrolled 1,002 dogs in a 40-day field study of Previcox. Side effects associated with firocoxib treatment were typical for the NSAID class and consistent with earlier studies that demonstrated a favorable tolerability profile for firocoxib relative to less selective NSAIDs. Responding owners rated firocoxib overall as convenient to administer and palatable, with 86% rating their dogs as happier or more active after starting treatment. The PET confirmed the results of registration and field trials conducted worldwide and demonstrated that under clinical conditions, client-owned dogs diagnosed with OA and treated with firocoxib experienced improvement in lameness and quality of life. Overall improvement of treated dogs appeared to increase with time over the 40-day study.

ACKNOWLEDGMENT

Merrial would like to thank all of the investigator practices that participated in this trial.

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^aOwner diary information and final blood test results were available for an additional three dogs that received medication throughout and completed the study. However, there was no final investigator or owner evaluation available for these dogs with submission of the raw data.

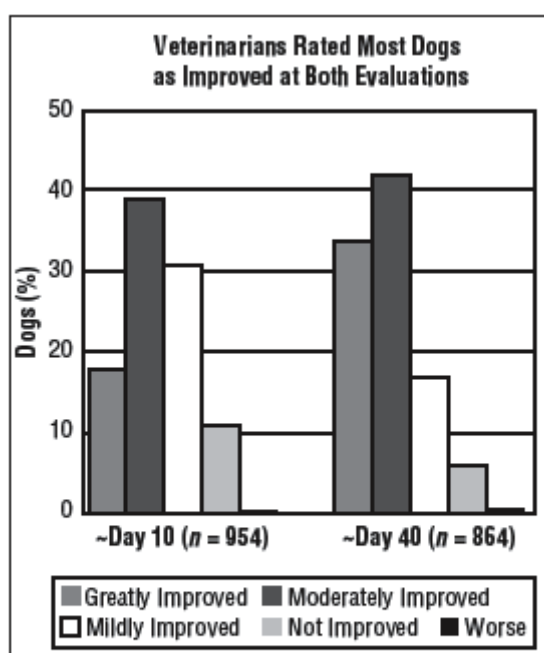


Figure 1. Investigator evaluation: ~day 10 and study end (~day 40). Expressed as a percentage of dogs presented on ~day 10 (n = 954) and ~day 40 (n = 864).

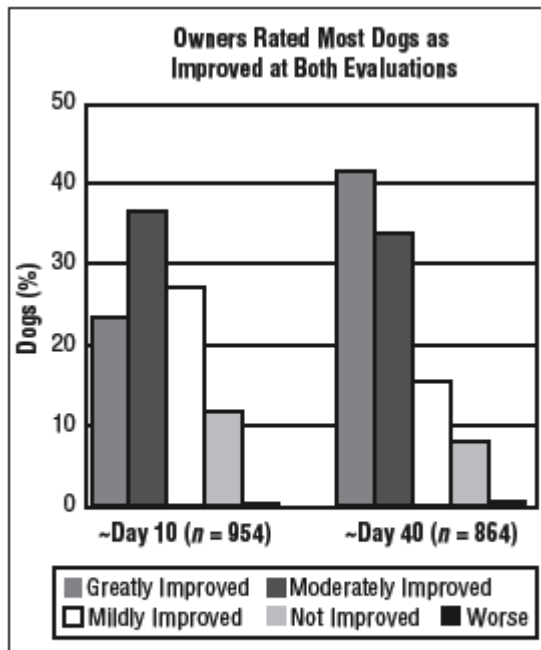


Figure 2. Owner evaluation: ~day 10 and study end (~day 40). Expressed as percentage of dogs presented on ~day 10 (n = 954) and ~day 40 (n = 864).

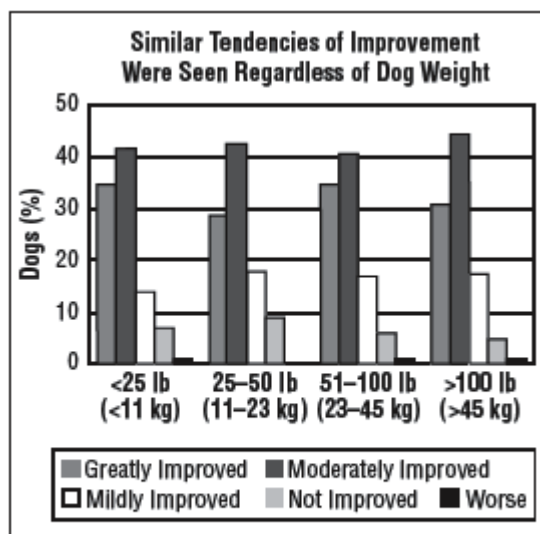


Figure 3. Investigator evaluation: Study end (~day 40) improvement by weight band.

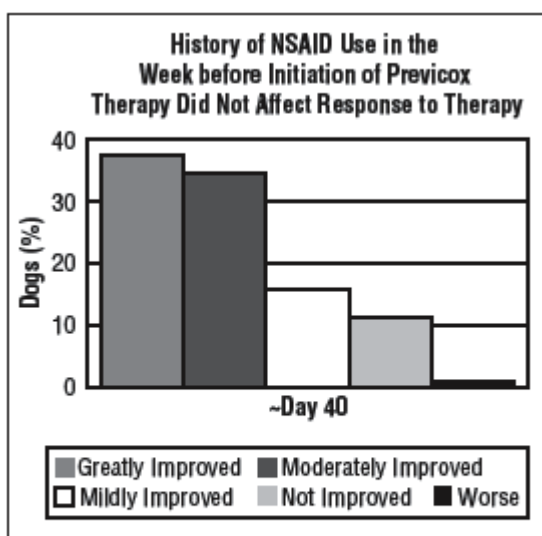


Figure 4. Owner assessment of improvement at study end (~day 40) in dogs taking carprofen, deracoxib, or meloxicam in the week before PET (n = 195).

TABLE 1. NSAID and Steroid Withholding Guidelines for Trial Participation

<i>Agent</i>	<i>Withdrawal Time</i>
NSAIDs	
Carprofen (oral)	2–3 d
Carprofen (injectable)	1 d
Deracoxib	1–2 d
Etodolac	2–3 d
Meloxicam	3–5 d
Tepoxalin	2–3 d
Aspirin	10–14 d
Steroids	
Short acting (hydrocortisone and cortisone)	2 d
Intermediate acting (prednisone, prednisolone, methylprednisolone)	7 d
Long acting (dexamethasone, triamcinolone, betamethasone)	4 wk
Repositol type (methylprednisolone acetate, triamcinolone acetonide)	6 wk

I have no intention of criticizing any particular author or organization specifically. I have chosen this particular article because it is

1. Freely available.
2. Has been promoted extensively as an important study by the organizations involved.
3. Provides a number of examples of common problems encountered in published studies.

Are the aims of the study clear and are the underlying assumptions of the study valid?

The introduction to the study does not clearly explain the aims of the study. A somewhat vague statement talks about veterinarians “gaining experience” and “familiarizing” themselves with the drug used. “Familiarity” and “experience” are neither measurable nor analyzable outcomes and thus right from the start it is not clear how to interpret the data generated.

Are the methods appropriate? In particular has there been adequate randomization, are selection criteria clear and unambiguous, are assessment methods objective or subjective, is the model a valid model of clinical occurrence?

Exclusion criteria were set by the organization arranging the trial however these criteria are not detailed in the paper. For example animals with “concomitant conditions such as gastrointestinal, renal or hepatic disease” were excluded however it is not detailed how such assessments were made. Were they based on blood testing, diagnostic imaging, histopathologic sampling or clinical experience? In addition investigators were also given the ability to make an arbitrary judgement based on “the needs of the patient” as to whether an animal was enrolled. Subsequently it is impossible to say whether or not there was any selection bias introduced and to allow for that in assessment and discussion.

A table of “washout” times for animals previously on medication is given however there are no references given for these times nor explanation of how they were derived.

Assessment is done using an ordinal scale. Whilst simple, ordinal scales (i.e. select one of 5 or 10 statements that describes a graduating scale) are statistically inferior to other linear scales

including visual analog scales (VAS). In addition this study has a biased scale i.e. there are more positive choices than negative choices. An ordinal scale should have an equal number of positive and negative choices as well as a neutral point. Finally the scale used can only be applied with reference to previous assessment (e.g. greatly improved, moderately improved etc.). Assessments at each timeframe should be able to be made independently to reduce the influence of bias and variability in memory.

The study enrolled animals between April and October in the northern hemisphere (United States) and followed them for 40 days. The dates may not seem relevant until one considers that this is the northern Spring / Summer / early Autumn. DJD is known to improve clinically in warmer weather and consequently one would expect improvement even without treatment. Given that the study model has no control, either positive or negative, then it is difficult to know how much of the improvement recorded is due to non pharmacologic factors.

Have the results been appropriately analysed? Have appropriate statistical tests been used. Are there mathematical errors in the results analysis?

Numbers should be presented as raw numbers not as derived assessments (e.g. percentages). In the study results when percentages quoted in the results for overall improvement are converted back to raw numbers it actually shows that, contrary to the statements in the results, the number of animals showing overall improvement fell from day 10 assessment to day 40 assessment according to both the owner assessment and veterinarian assessment (842 and 834 dogs improved at day 10 according to Investigators and Owners respectively versus 802 and 785 at day 40).

Routine biochemistry data from visits at day 10 and day 40 are not given nor is there any data from the owner diaries given. Owner adverse event diaries are often quite subjective and need to be processed to get usable information however there are methods for categorizing recorded events and then analyzing them according to standardized adverse event records.

Are the conclusions reached in the discussion justifiable from the data presented?

Due to the poor presentation of results data many of the conclusions in the discussion are also erroneous. The discussion

also fails to outline sources of variability in such a large study including inter veterinarian, variability between laboratories used for pathology testing, as well as environmental influences on outcome.

WHAT CAN WE BELIEVE THEN??

It is relatively easy to go through most studies and criticize them for some reason or another. That however does not mean that we should “throw the baby out with the bath water” so to speak. As long as sources of bias and variability are understood and accounted for then much information can still be garnered even from less than ideal studies. However as seen above it is important that the entire published study is looked at and not just the abstract or discussion. Critical appraisal and continued efforts to improve the quality of studies conducted will contribute greatly to our ability in future to conduct EBVM.

NOTES:

NOTES:

Therapies For Small Animal Hypertension

Dr Aitor Arteaga

Systemic hypertension is an increasingly recognised problem in feline (and canine) patients. Equipment for indirect blood pressure measurement is now readily available for clinicians facilitating the diagnosis of hypertension. Hypertension in cats and dogs is mainly associated to primary diseases such as renal disease and endocrine disorders such as hyperthyroidism, hyperadrenocorticism, hyperaldosteronism, diabetes mellitus and pheochromocytoma. Primary or essential hypertension is found less frequently, and in most cases the possibility of underlying renal disease cannot completely ruled out. Prevalence of hypertension in cats with predisposing diseases is high. Up to 20% of cats with renal disease have been reported to be hypertensive. Moreover, Syme and others (2003) reported that up to 22.5 % of hyperthyroid cats may develop hypertension following successful control of the hyperthyroidism. This is likely to occur due to unmasking of underlying renal insufficiency. The prevalence of hypertension in dogs with predisposing diseases remains controversial with some studies giving prevalences varying from 25% up to 90%.

Diagnosis and therapy of hypertension is important because sustained increased blood pressures can lead to organ damage. Hypertensive retinopathy and coroidopathy are the most common clinical manifestations recognised in cats. Hypertension may also affect other organs such as kidneys, heart and central nervous system causing further progression of renal disease, myocardial hypertrophy and hypertensive encephalopathy.

The non-invasive methods most commonly used in practice to assess the patient's blood pressure are the Doppler method and the oscillometric method. As indirect methods both have their limitations. The "white coat effect" is a major draw back of these techniques. Deciding when a patient has hypertension and when to treat is difficult in most occasions and recently the American College of Veterinary Internal Medicine produced a *consensus statement* (*J Vet Intern Med* 2007; 542-558) giving some guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats.

Therapy of hypertension has historically been associated with variable and inconsistent results. Drugs used in the past, included ACE inhibitors, diuretics and beta-blockers. Problems associated with these therapies included refractoriness of the hypertension to drugs, poor owner compliance and adverse effects of the multiple drug regimes.

ACE inhibitors remain the main recommended drug by most authors for dogs. However, in the last ten years the use of the calcium channel blocker amlodipine has become the cornerstone of the therapy of feline hypertension.

AMLODIPINE

Amlodipine is an arteriolar vasodilator. It is a member of the calcium channel blocker drug family. It has a long half-life in dog (up to 30 hrs) and a bioavailability of 88%. The characteristics of the amlodipine molecule are responsible for the gradual onset of action and a long duration of effect. This in turn reduces the possibility of acute hypotensive crisis. It reaches peak effect after 2-3 days.

Amlodipine is used extensively in human medicine. It is used alone or in combination with other drugs for the treatment of hypertension, ventricular hypertrophy secondary to hypertension and it has also been used in the setting of ischaemic heart disease.

There are no reports of the use of amlodipine in dogs with hypertension. However, there are multiple veterinary studies have been published in the last decade demonstrating the effectiveness and safety of Amlodipine in feline hypertension. The first published peer reviewed report (Henik and others 1997) was a prospective trial with 12 hypertensive cats divided in 3 groups: newly diagnosed hypertensive cats, cats on previous treatment with other drugs but no control of hypertension and cats on previous treatments that had secondary effects due to drugs used. Good control was achieved in most cats at a dose of 0.625 mg/cat (range 0.08-0.25 mg/kg) with only one cat needing more than 0.625 mg. The average systolic blood pressure dropped from 198 to 155 mm of Hg. No changes in blood creatinine or potassium or weight before or after treatment were noted in the cats of the study. Amlodipine was deemed to have a continuous and stable effect and to be a more consistent anti-hypertensive effect than other previously used drugs such as beta-blockers and diuretics. No cardiac (reflex tachycardia, hypotension) or renal (azotaemia) adverse effects were documented. A placebo-controlled,

randomized, blinded clinical trial by Snyder (1998) in 9 cats with naturally occurring hypertension showed similar results. Anti-hypertensive effect was noted at a mean dose of 0.18 ± 0.03 mg/kg with only 3 cats (all more than 5 kg) needing more than 0.625 mg of amlodipine. No signs of hypotension were reported in this study. Only one cat showed inappetence and weight loss although this was attributed to advanced renal disease. However, in this study no significant differences were found in blood urea and creatinine concentrations before and during treatment with amlodipine.

Amlodipine was also found to be effective in a long-term study of 30 cats with hypertension (Elliot and others 2001). Control of the hypertension (mean SBP before amlodipine was 202 ± 16.8 Vs 153.2 ± 21.6 during treatment) was achieved with amlodipine alone in 20 cats. The remaining 10 received amlodipine in combination with other drugs (propranolol, ACE inhibitors and/ or hydrochlorothiazide). Significant and durable reductions in systolic blood pressure were achieved. As in previous studies, no change in blood urea and creatinine was noted before and after amlodipine treatment. Interestingly no change in urine specific gravity was noted either despite significant reductions in blood pressure.

In humans side effects are rare. It can be used safely with other drugs such as beta-blockers or ACE inhibitors (Burges and Dodd 1990). Flushing and tachycardia are rare and in some studies incidence of these side effects were comparable to control group on placebo. Edema, muscle cramps and dizziness are more common in elderly patients but the incidence is still lower than when beta-blockers are used to control the hypertension (Burges and Todd 1990, Osterloh 1991). Hypotension (SBP: 75.6 mm of Hg) was documented in one cat on amlodipine in the study by Elliot and others (2001), although this cat was also receiving propranolol. Tolerance to certain antihypertensive drugs has been reported in humans during chronic treatment (Burges and Dodd 1990), although this has not been the case with amlodipine and cats (Elliot and others 2001). Hypokalaemia has been described in humans on amlodipine treatment (Reams and others 1987). A significant decrease in blood potassium concentration was found in a study by Elliot and others (2001). The same author recommends potassium assessment and supplementation in some cases to avoid development of severe hypokalaemia (Elliot 2002)

In humans on amlodipine therapy, improvement of glomerular filtration rate, effective plasma flow, and renal blood flow have been reported (Reams and others 1987). Despite the concern regarding the exposition of kidneys to hypertension when using amlodipine (due to preferential vasodilation of afferent renal

arterioles) blood urea and creatinine levels remain unchanged in all the feline studies and significant decreases in urine protein to creatinine ratio were found in the study by Jepson and others (2007).

The recommended dose varies from 0.1 mg/kg BID to 0.25 mg/kg (up to 0.5 mg/kg in cats).

ACE INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors bind to ACE competing with angiotensin I. This leads to angiotensin II (AII) production inhibition. The ACE inhibitors lead to decrease total peripheral resistance and a decrease in mean arterial pressure.

ACE inhibitors result in poor reductions of blood pressure in both dogs and cats (average reduction of 10 mm of Hg Vs 40 mm of Hg for amlodipine). Often despite its use, dogs will remain hypertensive and other drugs will have to be added to the regime (calcium channel blocker, beta blockers). However, there are still recommended for dogs with hypertension due to renal disease based on their preferential vasodilation of the efferent arterioles in the kidneys and their “renoprotective” effect, particularly in patients with glomerular disease and Proteinuria.

Adverse effects such as hypotension are rare. However, its use in dehydrated and/or hyponatremic patients may trigger nephrotoxicity and worsening of the azotaemia. Assessing renal function after initiation of ACE inhibitors in renal patients is mandatory. Other side effects include gastrointestinal signs such as vomiting and diarrhoea.

There are several ACE inhibitors available, including captopril, enalapril, benazepril, ramipril and imidapril. The main differences within these drugs lay in the duration of action and so dose and frequency varies depending on the drug. Doses of benazepril and enalapril are 0.5 mg/kg PO BID or SID depending on the species.

β-BLOCKERS

These are second line drugs, used when patients are refractory to drugs such as calcium channel blockers or ACE inhibitors or their combination. Atenolol is a selective β-1 adrenergic antagonist, with negative chronotrope and inotropic effects and also reduces the conduction of the sinoatrial and atroventricular nodes.

PRAZOSIN

Prazosin is an α -1 adrenergic-receptor (responsible for vasoconstrictive effect of the norepinephrine) blocking agent that causes both arteriolar and venous dilation. It may have some use in dogs with renal hypertension. Side effects include hypotension (mainly associated with the first dose), vomiting, diarrhoea, anorexia and syncope.

Dose: 0.5-2 mg/kg BID-TID. May be modified depending on response and blood pressure.

HYDRALAZINE

Hydralazine is a direct acting smooth muscle relaxant of the arteries and arterioles. It is very potent. Considered a tertiary option but it is a good choice for use in emergency hypertensive situations (0.2 mg/kg IV or IM). Most common side effect is hypotension particularly when used with other vasodilators such as ACE inhibitors. Blood pressure should be monitored (reduction of 10-50 mm of Hg are expected). Effect is noted within one hour and peaks 3 hours following administration. Net duration of effect is 12 hours. Other common side effects include gastrointestinal effects such as vomiting and diarrhoea. These effects can be managed by reduction of the dose.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

These drugs block the action of angiotensin II at the level of the receptors. Their main use is as anti-hypertensive in those patients that do not tolerate (cough) or cannot have ACE inhibitors. There are no controlled studies of these drugs in dogs or cats. Drugs of this group include Losartan, valsartan, olmesartan and irbesartan.

DIURETICS

In humans, diuretics and low sodium diets are can be effective in controlling mild to moderate hypertension. However they are not efficacious in controlling hypertension in small animals.

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NOTES:

Opioid Pharmacology and Clinical Applications In Cats and Dogs

Dr Sanaa Zaki

Attitudes towards pain, analgesia and opioids in particular have changed considerably over the past 10 to 20 years. Within the veterinary profession, numerous epidemiological studies have identified that the majority of veterinarians have an increased awareness of pain in companion animals and place greater importance on the provision of appropriate analgesia to animals with a painful medical condition or those undergoing a surgical procedure. Although the frequency with which veterinarians administer analgesics to cats and dogs has increased, there is still a disparity between the perceived incidence of pain in companion animals (according to both pet owners and veterinarians); and the frequency with which analgesics are actually administered. The difficulty in accurately assessing pain and inadequate knowledge of analgesic drugs may limit the ability of veterinarians to provide optimal pain management. This was highlighted in a 2001 survey of Canadian veterinarians¹, where although 62% of veterinarians that responded to the survey were using at least 2 classes of analgesics perioperatively; an over use of partial opioids and insufficient frequency of dosing was identified. This was despite more than half of respondents reporting that their knowledge of analgesia was “adequate”. In a 1999 survey of French veterinarians², less than 20% of respondents administered opioids to cats and dogs, with 73.7% of respondents sighting a lack of knowledge of opioid pharmacology as a reason for not using opioids. A survey of veterinarians in New Zealand³, found that the peri-operative use of analgesics ranged from 50% to 91% for surgical procedures, despite 58% of respondents considering their knowledge of pain assessment and treatment to be adequate.

The use of opioids to treat both acute and chronic pain is well established, and there are numerous opioids available each with different pharmacokinetic and pharmacodynamic properties. However, few opioids are licensed for veterinary use. Despite this, veterinarians have been using opioids to treat pain in animals for many years, often with limited knowledge of species specific opioid pharmacokinetics. The ability to map and characterise opioid receptors has improved our understanding of how opioids

exert their effect and has helped to explain some of the mechanisms behind the numerous species differences clinicians have observed.

To optimise the analgesic effectiveness of opioids and minimise undesirable side effects, veterinarians need to make informed decisions about which opioid to use and the frequency of dosing interval. This requires a good working knowledge of opioid pharmacology, including how opioid activity differs between species. For example, knowledge of opioid disposition in cats has increased in recent years, and veterinarians can now develop more appropriate dosing regimes, rather than make pain management decisions in cats that are based on extrapolation from other species such as humans and dogs.

OPIOIDS & OPIOID RECEPTORS

Opioids are any number of naturally occurring or semi-synthetic opium alkaloid derivatives, and other similar compounds which bind to opioid receptors on cell surfaces in the body, and whose opioid effects are blocked by opioid antagonists. Naturally occurring opioids such as morphine are found in opium (an extract of the poppy *Papaver somniferum*). Opioids are referred to as narcotic analgesics because of their ability to induce drowsiness and narcosis (sleep) in addition to their pain relieving effects. Morphine was first isolated from the opium poppy in 1806. In the 1970's opioid binding sites were identified in mammalian brains.

Based on current understanding, there are three classes of opioid receptors; μ , κ and δ . These receptors have also been classified as OP_3 (μ), OP_2 (κ) and OP_1 (δ) based on the order in which the receptors were cloned. For a period, a fourth class of receptor (σ) was thought to exist. However, it is now not considered to fit the criteria of an opioid receptor. Controversy continues about the exact number of opioid receptor classes, with some researchers believing that the ϵ receptor is another class of opioid receptor, acting as a binding site for endogenous opioid β endorphin. It has also been proposed that there are opioid receptor sub types, however, to date this has not been supported by cloning experiments.

Opioid receptors are located throughout the central and peripheral nervous system. Activation of opioid receptors exerts both excitatory (increased activity, vocalisation, manic behaviour) and depressive (analgesia, respiratory depression, bradycardia, sedation) effects. The overall effect varies between individuals and between species.

When an opioid is administered to an animal, three key processes determine the resultant outcome of the opioid/receptor interaction:

a. Selectivity

Which type of receptor does the drug act on?

Opioids can act at μ , κ , δ , or any combination of the three receptor types.

b. Efficacy

What is the intrinsic activity of the drug once it binds to the receptor?

Drugs can be pure agonists (inducing a maximal response once bound to the receptor); partial agonists (inducing a sub maximal response once bound to the receptor regardless of the dose administered); or antagonists (inducing no response once bound to the receptor). Some drugs are agonists at one receptor type and antagonists or partial agonists at another receptor type.

c. Affinity

How strongly does the drug bind to the receptor?

Opioids with a high affinity for the receptor (eg buprenorphine) have a long duration of action which is unrelated to the plasma half life of the drug.

Desirable effects = Analgesia and Sedation
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ANALGESIA

Analgesia is primarily produced by drug agonist activity at μ and κ receptor sites, but most predictably at the μ receptor site, with μ receptor selective agonists being the most effective analgesics.

The analgesic action of opioids is mediated via three mechanisms:

- Opioids block transmission of noxious stimuli by acting on pre and post synaptic receptors of primary afferent sensory nerves at the level of the spinal cord.
- Opioids block transmission of noxious stimuli and increase the amount of descending inhibition by acting on higher brain centres.

- Opioids block transmission of noxious stimuli by acting peripherally on opioid receptors generated in inflammatory conditions. Opioid receptors have been identified on nerve endings and inflammatory cells.

SEDATION

Sedation can be considered a side effect when using opioids primarily as analgesics. However, clinically this side effect is advantageous because opioids are frequently used as premedicants prior to induction of anaesthesia or simply as sedatives for fractious animals in order to facilitate handling and performing diagnostic or therapeutic procedures.

The most effective sedatives are reported to be butorphanol, pethidine and morphine.

Undesirable side effects = CNS excitation, bradycardia, hypotension, respiratory depression, vomiting/nausea, and gastrointestinal stasis

Central nervous system excitation

The intravenous use of some opioids can result in temporary overstimulation of the central nervous system (CNS). For example, rapid intravenous administration of morphine may cause a brief period of excitement, especially when used pre-operatively in an animal that is not in significant pain. “Opioid mania” which is reported to occur in cats, is based on a 1925 study by Joel & Arndts where cats that were administered morphine doses of 20mg/kg developed resultant CNS excitement.

Excitement in horses is also well documented, with animals demonstrating increased locomotor function, compulsive eating behaviour and agitation after opioid administration. Butorphanol, for example, can cause box walking and excitement type behaviour in horses, although combined use of sedatives will reduce this effect. Butorphanol has also been reported to induce a stress response in dogs when administered alone.

Despite the potential to cause CNS excitation, use of μ agonists in animals that are in pain will result in calming of the animal.

Respiratory depression

Respiratory depression is primarily a μ receptor action, and is mediated by a decrease in the sensitivity of neurones in the medulla to CO_2 and a delay in the response of the respiratory centre. It often manifests as a decrease in respiration rate (RR) rather than tidal volume (V_t), but not always. Partial agonists cause less respiratory depression than pure agonists, and will reach a ceiling effect. Respiratory depression is not as significant a side effect in animals as it is in humans especially where the animal is in pain. The respiratory depression effects may become significant when high doses of pure opioids are repeatedly used or when other CNS depressants been administered.

The panting that is seen with pure opioids such as methadone and fentanyl, is related to alteration of the thermoregulatory centre in the hypothalamus rather than a manifestation of respiratory depression.

Cardiovascular effects

Bradycardia, the main cardiovascular side effect, is centrally mediated (vagal) and can be reversed with the administration of atropine. Bradycardia is most marked with the rapid intravenous administration of high doses of pure μ agonists. Some opioids (morphine and pethidine) can cause histamine release when injected intravenously.

Mu agonists such as morphine cause mild hypotension (mediated via opioid receptors in the brain stem, which inhibit sympathetic tone to the heart). Venodilation (an effect of morphine), results in reduced preload, which may be beneficial in cases of congestive heart failure.

Gastrointestinal effects

Opioids cause an initial increase in gastrointestinal (GI) motility, with increased non-propulsive rhythmic contractions and an increase in smooth mm tone (including sphincter tone). This is followed by a period of GI stasis. Clinically, GI stasis does not appear to be a significant problem in cats and dogs. However, development of innappetence after 3-4 days of opioid administration (and beyond) may be attributable to GI stasis.

Partial agonists such as buprenorphine & butorphanol, have less GI side effects. Pethidine, although a pure opioid, has a spasmolytic action on the GI tract due to its anticholinergic like activity.

Nausea and vomiting, mediated through the CTZ, can occur after the administration of μ agonists. It occurs most frequently with morphine, when used in animals that are 'pain-free'. Butorphanol on the other hand has been shown to have antiemetic activity in both humans and dogs.

Other opioid effects

Opioids have an antitussive action at μ and κ receptors. There is an inconsistent association between analgesia and antitussive activity. Codeine and butorphanol are the most potent antitussives.

Pruritis is sometimes seen after epidural or intrathecal opioid administration. The itchiness is limited to caudal dorsum area. It is thought to be due to low doses of opioids enhancing C-fibre nociceptor activity.

Two pharmacokinetic effects of opioids which limit their use in humans are the development of '*acute tolerance*' and '*dependence*'. Acute tolerance, whereby a higher opioid dose is needed to produce the same pharmacological effect, has been demonstrated in animal studies where high doses of opioids are given to animals not in pain. However, it has not been demonstrated in the clinical setting, most likely due to the short periods that opioids are administered to animal patients (4-5 days). Unlike in humans where long term use is more common and the phenomenon is well recognised.

Dependence is defined as the need to continue drug administration after prior exposure to the drug, in order to prevent development of a withdrawal syndrome. Again this is not recognised in animals clinically, most likely due to the short-term clinical use of opioids in animals; although it has been studied and demonstrated in laboratory animals.

METABOLISM

Opioids are highly metabolised by the liver, with most opioids undergoing one or more of the following; glucuronidation, demethylation, dealkylation and hydrolysis. For example, 50% of morphine is conjugated with glucuronic acid by the liver. Buprenorphine is also extensively metabolised (metabolite

excreted in bile) with only 1% excreted unchanged in urine. Fentanyl on the other hand, although it is metabolised in liver, metabolites are excreted primarily in urine, with some clearance by lung tissue. Remifentanyl is unique in that it is metabolised by plasma esterases.

Some opioid metabolites also demonstrate a degree of activity (e.g. morphine-6-glucuronide is an active metabolite of morphine).

Opioids are generally well absorbed from the gastrointestinal tract but undergo extensive first-pass metabolism, resulting in poor bioavailability with both oral and rectal administration. For example, the bioavailability of morphine when administered both orally and rectally is approximately 20%.

Opioids are generally well absorbed via the intramuscular (IM) and subcutaneous (SC) route, although SC absorption is not consistent with all opioids in all species. For example, there is now evidence suggesting that SC buprenorphine is poorly absorbed in cats. Pethidine is also best given IM because it is difficult to achieve effect plasma levels via the SC route.

SPECIFIC OPIOID ACTIONS

Morphine

Morphine is a μ selective agonist that is both an excellent analgesic and effective sedative. Morphine has an elimination $T_{1/2}$ of 1-2 hrs, however it persists in CSF much longer than it does in plasma, therefore its duration of action is longer than suggested by its plasma $T_{1/2}$. The $T_{1/2}$ in cats is considerably longer (~ 3hrs) than dogs because of their liver's reduced ability to metabolise drugs which undergo glucuronidation. This not only results in a longer half life and therefore the need for less frequent dosing (~ every 4-6 hrs) compared to dogs, but also may explain why clinically, morphine appears to be less effective in cats; given that morphine's metabolites are also active.

Pethidine

Pethidine is a μ selective agonist with an atropine like structure. As a result it does not cause bradycardia and has minimal gastrointestinal side effects. In fact, its spasmolytic action makes it useful in animals with gastrointestinal disorders, pancreatitis and urolithiasis. Pethidine is less potent than morphine and has a shorter duration of action. The need for frequent dosing makes it a

poor choice for post operative pain management. Although, it's rapid onset of action and sedative properties make it useful as a premedicant. Pethidine should not be administered IV as it can cause significant histamine release and resultant hypotension.

Methadone

Methadone is a μ selective agonist. Although equipotent to morphine it appears to be a less effective sedative than morphine. However, when combined with a tranquiliser it does provide effective sedation. Unlike morphine intravenous injection does not cause histamine release, and vomiting rarely occurs when administered pre-operatively. Methadone has a long terminal $T_{1/2}$ (35 hrs) but its duration of action after a single dose is comparable with that of morphine (4-6 hours). Care should be taken with repeated dosing or continuous infusions, as accumulation will occur.

Fentanyl

Fentanyl is a potent μ selective agonist. At therapeutic doses respiratory depression and bradycardia is more marked than morphine and methadone. It has a rapid onset of action (2-5 minutes) and a short duration of action (5-20 minutes) after a single dose. Fentanyl has a large volume of distribution and a high clearance value (with inactive metabolites), but a relatively long elimination $T_{1/2}$ (3-5 hrs). This is because it deposits in fat and is then slowly released. Because of its short duration of action, fentanyl is often administered as an infusion. Accumulation becomes significant after infusions of > 2 hrs. When used intra-operatively, inhalational requirements are significantly reduced in both cats and dogs.

Hypnorm is a neuroleptanalgesic combination containing fentanyl and fluanisone, commonly used in small mammals. Innovar is another neuroleptanalgesic formulation combining fentanyl and droperidol.

Alfentanil

Alfentanil is a potent μ selective agonist. It has a short elimination $T_{1/2}$ (0.4 – 2hrs), a small volume of distribution and a moderately fast clearance rate. Duration of action is 2-5 minutes and so is best used as a continuous infusion. Pretreatment with atropine and ventilatory support is recommended. Alfentanil has been shown to greatly reduce anaesthetic maintenance requirements.

Buprenorphine

Buprenorphine is a μ selective partial agonist. It has a slow onset of action (30-60 minutes for peak effect) regardless of the route of administration. Buprenorphine binds to and dissociates from the μ receptor very slowly. Its high receptor affinity makes reversal and concurrent use of other opioids less effective. Buprenorphine has a long elimination $T_{1/2}$ (42 hrs in dog), a large volume of distribution and a moderately fast body clearance. Clinically it has a moderate duration of action (4-8hrs). SC administration does not result in fast enough uptake to achieve a sufficient concentration gradient that allows adequate concentrations to reach the effector site. For this reason, IM injection is recommended unless a loading dose has previously been administered.

Butorphanol

Butorphanol is a μ selective weak antagonist and κ selective agonist. It is an effective sedative with a rapid onset of action, and reduces anaesthetic requirements when used pre-operatively. However, it has limited analgesic effects, with poor efficacy for somatic pain, and analgesia duration of action of only 1-2 hrs. It partially reverses the analgesic and respiratory depressant effects of pure μ agonists.

Naloxone

Naloxone is μ , κ and δ selective antagonist. Its duration of action is approximately 60 minutes. Naloxone is a competitive antagonist that reverses all pure opioid effects, by displacing other opioids and binding to opioid receptors without exerting any agonist effect. Interestingly, naloxone is also indicated as an adjunct treatment for hypotension in the management of septic and endotoxic shock.

Opioids are unique in that they demonstrate different pharmacological effects depending on whether pain is present or absent.

CLINICAL APPLICATIONS

1. Premedication and sedation: opioids are effective sedatives in addition to their analgesic activity
2. Pre-emptive analgesia: pre-emptive activity of opioids has been demonstrated with pethidine in dogs, and in rodents, but the pre-emptive effect is controversial in humans.
3. Intra-operative administration: an anaesthetic sparing effect has been demonstrated for fentanyl, morphine and other opioids in both cats and dogs.
4. Post –operative and non surgical pain: Opioids are a class of analgesics that offer numerous options for managing pain in animals.

Opioids can be used to treat mild, moderate and severe pain states. Duration of action ranges from a few minutes to several hours, depending on which drug is selected. In addition to traditional routes of administration (SC, IM and IV), opioids can be effectively administered via the transdermal (fentanyl), transmucosal (Buprenorphine), oral (morphine and butorphanol), intra-articular (morphine), epidural (morphine, pethidine) and intrathecal routes.

STRATEGIES TO OPTIMISE EFFECTIVE USE OF OPIOIDS TO TREAT PAIN

1. Adopt a multi modal approach to pain management that utilises both pharmacological and non-pharmacological strategies.
2. Titrate opioids “to effect” based on the degree of pain the animal is assessed to be experiencing.
3. Consider rotating opioids in cases where continuous use of one opioid is no longer effective.
4. Make use of non traditional routes of administration to increase efficacy and animal compliance.
5. Consider concurrent use of sedatives. This may enhance the analgesic effect of opioids in some animal patients

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NOTES:

Management Of Hyperadrenocorticism In The Dog

Dr Jody Braddock

Canine hyperadrenocorticism is the most common endocrine disease of adult dogs. It is a syndrome caused by excessive circulating concentrations of glucocorticoids that have global effects on the body. There is not an organ system, or metabolic function that is not affected either directly or indirectly, in some way. The main effects of glucocorticoids are:

- Gluconeogenesis
- Lipolysis
- Protein catabolism
- Anti-inflammatory effects
- Immunosuppressive effects

AETIOPATHOGENESIS OF HYPERADRENOCORTICISM IN THE DOG

Adrenal tumours

Spontaneous mutation and uncontrolled growth of (? monoclonal) population of adrenocortical cells.

Pituitary-dependent disease

Multiple theories have been proposed as to the cause of pituitary dependent hyperadrenocorticism (PDH) in people and dogs.

The most feasible hypothesis is that clonal expansion of a single aberrant cell results from random mutation and causes development of a pituitary adenoma or adenocarcinoma. This is supported by DNA analysis that showed that almost all human pituitary tumours consist of a monoclonal cell population – and given the many similarities between human and canine disease, it is likely that this is also the case in dogs.

Another theory proposes abnormal pituitary control by the hypothalamus or its products. This could occur due to increased CRH secretion, or abnormal pituitary responses to it. Alternatively, the abnormality could lie with the secretion or effect of the inhibitory neurotransmitter dopamine or other biogenic amines. Despite extensive research however, there has been little to support these theories, and a reasonable amount of data that would seem to contest them.

In humans, it has been found that small, non-functional microadenomas are relatively common at necropsy (11-23%) but only manifest clinically in 0.002 – 0.025% of the population (Burrow et al 1981, Molitch & Russell 1990). In a similar epidemiological survey in a colony of geriatric beagle dogs, 10% of those over 6 years of age had pituitary tumours, of which about half (51%) had clinical evidence of a hyperfunctioning pituitary-adrenal axis (Berry et al 1994). Thus it would seem that pituitary tumours are common in people and aged dogs, but are more likely to be functional in the latter.

A third theory which combines both the above hypotheses is that there is an initiating or hypophyseal cause of pituitary tumour growth (quite probably cell mutation and clonal expansion) that may or may not be followed by a ‘promoting’ factor or factors, such as abnormal hypothalamic or higher controls. This would account for the large number of subclinical tumours occurring in dogs presumed to lack the ‘promoting’ factor, and the comparatively smaller group of dogs with clinical disease. It has been suggested that the higher percentage of dogs with tumours manifesting clinically indicates that ‘promoting factors’ may be different, or more common than those operating in people (Bruyette et al 1997).

Three causes of hyperadrenocorticism in the dog

1. Pituitary dependent (85% dogs) - usually a benign tumour secreting excessive amounts of ACTH
2. Adrenocortical tumour - 50% benign; 50% malignant
3. Iatrogenic - excessive administration of exogenous steroids over a long period of time

Hyperadrenocorticism signalment

- Middle aged to older dogs
- Slightly more female than males affected
- Breed predisposition?
 - Poodles, Dachshund, Terriers, Beagles, GSD, +/- Boston Terriers and Boxers
- Weight?
 - 75% dogs with PDH are <20 kg.
 - 50% dogs with adrenocortical tumours >20 kg

Hyperadrenocorticism is a *clinical syndrome*, not a laboratory diagnosis.

Animals must have a history and clinical signs to make the diagnosis. A “diagnostic” endocrine test is NOT a diagnosis in the absence of supportive clinical findings.

Most animals will have some, but not all of the historical, clinical and laboratory features of the syndrome.

Beware: False Diagnosis!

- Any condition that causes physiological or psychological stress can lead to false positive diagnosis of hyperadrenocorticism. ACTH secretion and elevated circulating cortisol levels are the animal’s natural response to stress. Similarly, any veterinary procedure conducted within a week, or during endocrine testing will affect (and generally negate) the results
- Cross-reaction of exogenous glucocorticoids and/or their effect on the pituitary-adrenal axis will also cause erroneous results

TREATMENT OF ADRENAL TUMOURS

Surgical excision of affected adrenal gland is the treatment of choice. It should be considered essential that this be undertaken in a referral environment with both specialist surgeons and internists to provide the best outcome for the patient. These patients can be extremely demanding surgically, and with respect to peri-operative care and monitoring. Peri-operative morbidity (and mortality!) is

very dependent on the amount of surgery time, tissue handling, vascular occlusion, haemostasis and pre-operative patient preparation. These patients do require 24 h veterinary care, in-house facilities for electrolyte, glucose, blood pressure and other monitoring (eg blood gas analysis) as well as the equipment for multiple transfusions (cortisone acetate, morphine, heparin, fresh frozen plasma etc), and the expertise in anticipating and detecting post-operative complications.

The main risks of surgery are pulmonary thromboembolism, (or other thromboembolic events), haemorrhage, hypoadrenocorticism crisis, and post-operative pancreatitis. Less serious complications include slow wound healing and wound infection.

Malignant vs benign tumours? It is difficult (impossible?) to distinguish pre-operatively whether a tumour is benign or malignant, unless it is showing biologically aggressive behaviour, such as local invasiveness or obvious metastatic disease. Even histopathology post-operatively can be equivocal since endocrine tumours are very difficult to classify histologically.

Malignant tumours grow slowly, and although have often microscopically metastasised by time of removal, commonly do not cause clinical signs for some time after surgery since they are relatively slowly progressive tumours. Average survival time is 36 months for *all* dogs that undergo successful adrenalectomy (Feldman & Nelson 2004). This includes dogs that have adrenal adenomas and carcinomas.

Trilostane is very useful to treat dogs with adrenal tumours – it has a place particularly for preparing the patients for surgery. In markedly affected patients, one to three months treatment with trilostane prior to surgery can make the patient a much better surgical candidate and considerably reduce the peri-operative risks.

Trilostane tends to be more effective in treating hypercortisolaemia associated with adrenal tumours, than PDH, due to adrenal tumour dogs not having pituitary over-ride of adrenal suppression as occurs in PDH. Lower doses tend to be required for dogs with adrenal tumours.

Trilostane has also been reported to be used for dogs with metastatic adrenocortical tumour disease, with good survival times (10, 11 and 17 months) (Benchekroun et al 2008) which surpasses that for mitotane used in the same way (Kintzer & Petersen 1994).

TREATMENT OF PDH

Reduce ACTH secretion

- Hypophysectomy?
- Selegiline
- Bromocriptine
- Cyproheptadine

Selegiline

Monoamine oxidase-B inhibitor acting centrally as a dopamine agonist, theoretically suppressing ACTH secretion from the pituitary.

- a safe drug but ineffective in treating dogs with PDH

Reduce adrenal cortisol production

- o,p'-DDD (mitotane)
- Ketoconazole
- Trilostane
- Metyrapone
- Adrenalectomy

Mitotane

o,p'-DDD is an isomer of p,p'-DDD and chemically related to DDT - both insecticides.

Mode of action

Mitotane has a direct cytotoxic effect on mitochondria of adrenal cortical cells to induce cell necrosis of the zona fascicularis and reticularis (the zona granulosa is spared). It also interferes with steroid synthesis by adrenal cortical cells and has effects on extra-adrenal steroid metabolism.

Selective cytotoxicity is due to selective binding to ACTH receptors, conversion to active metabolic intermediates within zona fasciculata/reticularis, and selective covalent binding of those metabolites to mitochondria.

Pharmacokinetics

- Poor systemic bioavailability
- Enhanced by presence of food
- Better absorption in hyperadrenocorticoid dogs
- Higher bioavailability in small dogs c.f. large dogs
- Higher bioavailability of ground/powdered tablets
- Pure drug dissolved in maize oil has the highest bioavailability

Clinical use

Mitotane is used to induce controlled destruction of the zona reticularis and fasciculata of the adrenal cortex, ideally sparing the zona glomerulosa (mineralocorticoid secretion).

- Loading dose
 - 50mg/kg/day (divided)
 - Must be given with food
 - ≤5 days treatment then stop, wait 2 days then test responsiveness to ACTH
 - Repeat this process until mild early signs of hypoA OR until adequate suppression of adrenal function on ACTH stimulation test
 - Maintain contact with the client, and dispense cortisone acetate for emergency use

***** Animals can die during mitotane induction treatment *****

- Maintenance dose
 - ~ 50mg/kg/week (divided)
 - Must be given with food
 - Test after 1 month then every 3 months
 - May require ↑ or ↓ of 25% maintenance dose
 - Sometimes a repeat “pulse therapy” is required
 - Sometimes have to re-induce
 - Sometimes have to withhold drug if over controlled
 - Occasionally induce hypoadrenocorticism
- “Alternative” mitotane protocol - planned induction of permanent hypoadrenocorticism by chemical ablation

Monitoring Response to Treatment

Patients are monitored by both their clinical signs, and ACTH stimulation testing. The aim of mitotane therapy is to induce iatrogenic hypoadrenocorticism. Aim for 0 hour and 1 hour cortisol concentrations between 25 – 75 nmol/L.

What can go wrong with mitotane treatment?

Direct adverse drug reactions occur in about 25% dogs treated with mitotane. Generally these are mild and resolve when the mitotane is withheld. They usually manifest as gastrointestinal signs (vomiting, diarrhoea and/or Inappetence), lethargy, and/or neurological signs such as ataxia or depression. Hepatotoxicity is very rare. With the exception of hepatotoxicity, most dogs will not have recurrence of these signs if the dose is divided into smaller doses, +/- spread out over a longer time. Some individuals will not tolerate the drug at all and alternative treatments should be used.

Hypoadrenocorticoid crisis - iatrogenic hypoadrenocorticism

- Medical emergency
 - Vomiting
 - Anorexia
 - Diarrhoea
 - Collapse

Subacute hypoadrenocorticism

- Less dramatic – “ain’t doin’ right”
- Inappetent
- Lethargic

Managing iatrogenic hypoadrenocorticism:

Mild cases

- Cortisone acetate 0.5 - 1.0 mg/kg PO q 8 - 24h
- +/- fludrocortisone 0.02 mg/kg PO q 24h
- 12 - 24h “washout time” required before ACTH stimulation test

Severe Addisonian crisis requires immediate hospitalization, intravenous fluids, hydrocortisone CRI and other adjunctive care and monitoring.

Hyperadrenocorticoid dogs experiencing an Addisonian crisis during treatment require more exogenous cortisone to maintain the same blood levels as a normal or hypoadrenocorticoid dog. This is because they are highly efficient at metabolising cortisol molecules due to up-regulation of the steroid metabolising enzymes and pathways.

“Relative hypoadrenocorticism”

This occurs when the dog suddenly drops from very high circulating cortisol concentrations to normal cortisol concentrations. They show mild hypoadrenocorticoid signs but an ACTH stimulation test demonstrates ideal control of the hyperadrenocorticism. These patients may need very short-term treatment with cortisone acetate - usually no more than a week or two. The drug is tapered slowly and stopped when the dog appears to be well again.

Drug resistance

If drug resistance is suspected, review the original diagnosis – the most common cause for failure to induce is that the dog is not in fact hyperadrenocorticoid! Normal dogs are much more resistant to the effects of mitotane than hyperadrenocorticoid dogs.

- Review client administration
- Drug expired? Stored correctly? Batch?

Improving safety

- Individualise treatment for every patient
- Induce in 5 - 7 day steps – never dispense more than a week’s worth of medication at a time during the initial induction period
- Provide access to 24 h veterinary phone advice and veterinary treatment should that be required
- “Antidote” (cortisone acetate) dispensed for home use
- Veterinarian’s familiarity with drug

Cost of mitotane treatment

A 20kg dog costs ~ \$2000 pa for maintenance treatment. This assumes you are administering ~ 50mg/kg/week and are monitoring with a consultation, physical examination and ACTH stimulation test every 3 months. A 5 kg dog costs ~ \$1200 pa for maintenance treatment.

Discussion of costs is often overlooked when discussing treatment of hyperadrenocorticism with owners. For some owners the long term costs are a factor when deciding whether to treat their pet or not.

Other considerations when using mitotane

- Off label dispensing
- Drug availability
 - Single world-wide source (Italy)
 - Drug drought of ~ 1999 - 2000!
- Owners must be advised that they are handling cytotoxic drug and informed of safe handling procedures
- Care with clinic staff exposure

There are not significant differences between the survival times for animals treated with trilostane and those treated with mitotane (traditional protocol). Only age at diagnosis and weight are significantly negatively associated with survival (Barker et al 2005).

****** Clemente et al 2007 found longer survival times for trilostane compared to mitotane when the latter was used for non-selective adrenocorticolysis.

Trilostane

Trilostane is a synthetic, hormonally inactive steroid that competes with pregnenolone as a substrate for 3- β -hydroxysteroid dehydrogenase (3 β -HSD) and thus inhibits conversion of pregnenolone to progesterone. It is therefore a non-selective inhibitor of almost all steroid hormone production including adrenal, gonadal and placental sources. Inhibition of adrenal steroidogenesis has been shown to occur at lower doses than that required to inhibit steroidogenesis in other organs. It is interconverted in vivo to an active metabolite 17-keto-trilostane which has 1.71 times the biopotency of the parent compound. Excretion is mainly in bile, but also to a lesser extent in urine.

It has also been reported in rodent models, that trilostane alters the expression of glucocorticoid receptors on the cells of target organs, even when circulating glucocorticoid levels are unchanged (Malouitre et al 2006). If this were also the case in dogs, it would be expected to have beneficial effects in treating hyperadrenocorticoid patients by reducing the effect of cortisol at the tissue level, as well as decreasing circulating blood concentrations of cortisol.

There are (to date) no pharmacokinetic studies in dogs. In people there is substantial individual variation in absorption, metabolism and clearance rate. The reason for this is unknown. Also, the clinical effect in people with Cushing's syndrome varies substantially. Plasma drug levels may more accurately reflect pharmacological effect than the dose rate being administered.

A frequent observation has been that dogs have an initial 'sensitivity' to trilostane that is of rather short duration, and the dose then has to be increased until the appropriate dose for longer-term use is reached. The time required to reach this final dose varies between dogs, but the trend is for the requirement to eventually 'plateau', so perpetual upward dose adjustment is not needed. The loss of initial sensitivity may be caused by induction of certain enzymes that metabolise trilostane and its metabolites, up-regulation of competitively blocked enzyme pathways, or initial ACTH over-ride of the partial blockade.

There is variation in dose rates required for individual animals, and in the duration of drug dose effect for each dog. A starting dose of 10 mg/kg is recommended, with upward or downward dose adjustment to achieve an ACTH response at 4 - 6 hours post-trilostane administration (time of peak effect) that indicates adequate adrenal suppression. The dose most likely needed to control PDH will be around 16 - 19 mg/kg, once or twice daily, with larger dogs tending to require a lower dose in mg/kg than small dogs. The most expedient means of judging adequate duration of effect is measurement of UCCR in a urine sample collected at home before dosing the animal (whether the dosing is 12-hourly or 24-hourly). A high UCCR suggests escape from control of PDH in an interval shorter than the dosing interval. A brief period of 'escape' indicated by mildly increased UCCR is probably not important for overall control of the disease. It is not known for what proportion of the day that it is necessary to maintain adrenal suppression in order to satisfactorily treat PDH. At present, clinical response to treatment serves as the best guide to treatment adequacy.

Treatment guidelines

Trilostane is given once daily initially.

Initially, dogs weighing <5 kg receive 30 mg, those 5 – 19.9 kg receive 60mg, and dogs ≥ 20 kg receive 120 mg. The drug is given in the morning if given once daily to facilitate testing at time of peak effect (4 – 6 h post-dose). Drug absorption is not affected by food.

Owners are asked to present their dogs for recheck at days 10, 40, and 120 of trilostane treatment, and thereafter at least every 3 months. They are requested to bring a voided urine sample from the dog, collected just prior to dosing with trilostane. At each visit owners are asked for their observations on the dog's general health, thirst, appetite, activity levels, panting, and any abnormal events such as vomiting or behavioural changes. Owners are also asked to monitor their dog's water intake over a 24 hour period prior to each visit if possible.

An ACTH stimulation test is performed 4 – 6 hours after trilostane dosing (the time of peak effect).

An adjustment is made to the dogs' trilostane dose if the ACTH stimulation test results indicated inadequate or excessive control (aim for 0-h and 1-h cortisol between 20 – 75 nmol/L at peak effect).

For dogs weighing ≥ 10 kg, the dose change is usually in increments of 60 mg, and in dogs weighing <10 kg the increments are 30 - 60 mg, depending on the degree of adrenal suppression or release thought to be required.

If the dose is adjusted, the owner is asked to return the dog for an additional recheck, an ACTH stimulation test, and UCCR determination in 10 – 14 days. This process is repeated until a satisfactory ACTH stimulation test result is obtained. Rechecks are then at one month and then 3-monthly.

The UCCR is used to roughly gauge the duration of drug effect. This is extremely variable between individuals (varying from 8 – 24 h). A high UCCR just before dosing (i.e. $\text{UCCR} > \sim 30 - 40$) may indicate that twice daily dosing is required. In this case I may get the animal back for an ACTH stim test at 12 – 14h post-dose to assess duration of effect OR as I became more experienced with the drug, if clinically indicated (apparently poor overall clinical response to trilostane despite apparent good control at time of peak effect) I will often simply change to twice daily dosing and continue as above.

Some (most?) individuals will become iatrogenically hypoadrenocorticoid after months to years of treatment on trilostane. In most cases this is detected on routine rechecks but occasionally an animal will present for lethargy, inappetence/vomiting or rarely an Addisonian crisis. This hypoadrenocorticoid state endures for variable periods of time (a day to a year or more!). In some cases a significant dose reduction is required. In others, the drug needs to be withdrawn completely until adrenal function recovers. The cause for this phenomenon is unknown and cannot be rationalised based on the known pharmacological actions of this drug. It may be that adrenal necrosis of varying degrees is the underlying reason for this - but the cause of the adrenal necrosis in trilostane treated dogs is not currently known. It may be an effect of increased circulating concentrations of ACTH. Adrenal hyperplasia seen in trilostane treated dogs may predispose these patients to adrenocortical cell apoptosis/necrosis. Alternately trilostane or its metabolites may be toxic to adrenal cortices.

Cost of trilostane treatment

A 20kg dog costs ~ \$4500 – 5200+ pa. This assumes you are administering ~ 12mg/kg/day (with 50% drug mark-up) and are monitoring with a consultation, physical examination and ACTH stimulation test +/- UCCR every 3 months. If the dog has to be on twice daily dosing then this will significantly increase the cost. A 5kg dog would cost ~\$2000 – 2300 pa if once daily dosing.

Other treatment protocols

Dr Feldman and his co-workers at UCLA, Davis report relatively frequent adverse effects (32% patients) and death (9%) when they used trilostane doses of 3 – 6mg/kg PO q 24h to treat a small group of 22 dogs with naturally occurring hyperadrenocorticism (PDH and AT) and a rate of illness of 17% across several other studies collectively (Vaughan 2008). With the rationale that the occurrence of adverse effects was unacceptably high, (as it indeed was as reported here) and because hyperadrenocorticism is usually “neither a rapidly progressive nor life threatening condition” they adopted a low-dose twice daily treatment protocol for which “the primary goal of treatment ... is to achieve resolution of signs of the condition, as perceived by the owners”. In this protocol a dose of 0.5 – 2.5 mg/kg PO q 12h was administered over a 4-month period. A favourable report from the owners and a post-ACTH stimulation cortisol value of 150 nmol/L or less was considered to indicate

adequate endocrine control. Even at this dose, 2 of the 22 dogs were ill, (with hyponatraemia and hyperkalaemia), required hospitalisation, IV fluids and both owners refused to resume treatment with trilostane. In these dogs the post-ACTH cortisol values were 36 nmol/L and 126 nmol/L. The authors concluded that a percentage of dogs treated with trilostane have adverse effects “associated with factors other than dose or frequency of administration”, but that dosing with the lower dose of trilostane twice daily resulted in a lower incidence of adverse effects while (in their opinion) effectively managing the disease.

What can go wrong with trilostane treatment?

In my own experience of using trilostane since 1999, adverse effects are not common, are generally mild, and easily managed. This is with the rare exception of acute adrenal necrosis, which has been reported to occur at various times in relation to starting trilostane – and if severe, presents as a hypoadrenocorticoid crisis. It may or may not be related to the trilostane dose, frequency of dosing and/or duration of treatment.

Iatrogenic hypoadrenocorticism

A relative overdose of trilostane will cause signs of hypoadrenocorticism, as listed above for mitotane treatment. Iatrogenic hypoadrenocorticism tends to occur less often, and less dramatically than with mitotane because the effects of trilostane peak at 4 – 6 hours after the dose is administered, but wane through the rest of the 24 hour (or 12 hour) dosing interval – exposing the dog to higher concentrations of circulating cortisol during the rest of the day. The difference between trilostane and mitotane is that (excepting cases of adrenal necrosis), withdrawal of trilostane for 24 – 48 hours will usually resolve hypoadrenocorticoid signs, and supplemental glucocorticoids may or may not be required. Trilostane is a competitive enzyme inhibitor, so once it is metabolised, it will not longer exert an effect – unlike mitotane that induces adrenal cortical lysis, which can take weeks or months to recover.

Having said this however, although most patients are well within a day or so of ceasing trilostane treatment, in some cases it can be weeks before they revert to hyperadrenocorticoid signs and endocrine function. These dogs will often then require lower maintenance doses of trilostane for ongoing management. The cause of the delayed return to hypersecretion of cortisol and

subsequent increased sensitivity to trilostane is not understood. Perhaps it may be due to partial adrenal necrosis or other toxicity of the drug on the adrenal cortices?

It has also been observed that some dogs with hyponatraemia, hyperkalaemia and signs of malaise have cortisol concentrations on ACTH stimulation tests results not usually associated with hypoadrenocorticoid signs. These individuals would seem to have mineralocorticoid pathways more sensitive to trilostane suppression than glucocorticoid pathways.

Gastrointestinal signs and malaise

Rarely, some dogs will have signs of inappetence, vomiting and/or diarrhoea but adequate adrenal function on endocrine testing. Withdrawal of trilostane for 1 – 2 days will resolve the signs and dogs can often be started back on trilostane at an adjusted (lower) dose.

Adrenal necrosis

This has been reported to occur days to months after starting trilostane treatment. These patients may present with hypoadrenocorticoid signs, (Chapman et al 2004) or if the necrosis is only partial, there may not be hypoadrenocorticoid signs (Reusch et al 2007).

OTHER TREATMENTS

Ketoconazole

Side effects are common with this drug, it is relatively expensive to use at the doses required, and it is ineffective in more than 20% of patients.

Bilateral adrenalectomy

This is a relatively costly option but represents a “one off cost” to the client. It can be more economical in large dogs over their lifetime (compared to medical treatments). Some animals more

stable when being treated as an iatrogenic hypoadrenocorticoid patient, particularly compared to some patients treated with mitotane. This treatment obviously makes the patient permanently hypoadrenocorticoid, and they then have an absolute dependence on medication for life – client selection is very important! Owners must be consistent with administration of medication and vigilant in watching for signs of hypoadrenocorticism. This treatment requires specialist surgery and perioperative medical management.

Benign neglect

Pituitary dependent hyperadrenocorticism is not in itself life threatening unless rare complications develop, and even malignant adrenocortical tumours generally do not behave biologically aggressively and progress slowly. Quality of life can, however, deteriorate as the syndrome progresses. The problems that usually have the most impact on quality of life are mental dullness, progressive muscle atrophy and weakness, neuropathies, respiratory signs and exercise intolerance, obesity, increased frequency of opportunistic infection or parasitism including demodicosis, other skin problems (calcinosis cutis) - and sometimes severe polyuria, polydipsia and polyphagia can be intolerable to owners and this becomes the life-threatening condition. In other cases, the effects of hyperadrenocorticism can secondarily impact on other diseases in the patient – for example the effect of systemic hypertension on degenerative mitral valve disease or renal failure, or the effect of hypercortisolaemia and/or obesity on control of diabetes mellitus.

Some individuals have underlying inflammatory conditions such as degenerative joint disease, allergies and other immune-mediated disease, myelopathies – and these can be unmasked by treating hyperadrenocorticism, due to the resulting decrease in circulating cortisol levels. The dog that previously “self treated” may suddenly have other problems that impact on its quality of life more than the hyperadrenocorticism did. Often these other problems can be effectively managed medically or in other ways – sometimes they cannot, and consideration needs to be given to withdrawal of treatment.

Other patients are not suitable for treatment due to cost constraints or other owner factors such as an inability to monitor the patient adequately or administer medications reliably.

Another group of patients that may qualify for “benign neglect”, at least initially, are those that have been diagnosed with hyperadrenocorticism, but show only very mild signs of their

disease. For example patients that have had blood biochemistry changes identified on pre-anaesthetic profiles, which are then followed to a diagnosis of hyperadrenocorticism. It is appropriate to discuss with the client the potential benefits and any negatives to treating the dog, and the ways in which treatment will improve its quality of life (or otherwise). It can be difficult to justify the expense and the necessary monitoring and cost to the owner if appreciable improvements to the dog's general health and quality of life cannot be identified. Sometimes it is preferable to suggest 6 monthly recheck visits to review the patient and discuss treatment when it is deemed necessary.

REFERENCES AND FURTHER READING

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Treatment Of CNS Inflammatory Disease (GME) In Dogs

Dr Georgina Child

Inflammatory diseases of the CNS can affect the brain, meninges and /or the spinal cord. Most disease processes causing meningitis also cause an associated encephalitis and or myelitis in animals. Non infectious and presumed immune mediated forms of meningoencephalomyelitis are much more common in dogs than infectious causes. In most immune mediated conditions the cause of the immune system abnormality is not established. Presumed immune mediated diseases include granulomatous meningoencephalomyelitis (GME), corticosteroid responsive meningoencephalomyelitis, necrotising vasculitis, breed specific necrotising meningoencephalitis (pug dog, maltese, chihuahua) and necrotising leucoencephalitis (yorkshire terrier). A definitive diagnosis is made on histopathology and in most cases an ante mortem diagnosis cannot be made as clinical signs and results of diagnostic tests are often very similar, and also may be indistinguishable from infectious causes of meningoencephalomyelitis, vascular diseases and some neoplastic diseases of the CNS without histopathology. These histopathologic distinctions in non inflammatory meningoencephalitis may or may not represent different underlying causes (or immune mechanisms). The term GME has often been used to include all of these noninfectious CNS inflammatory diseases although the pathology may not be the same. The terms meningoencephalitis (or meningoencephalomyelitis) of unknown aetiology (MUA) has been proposed as a more accurate diagnosis. Other proposed or previously used descriptions include non pathogenic meningoencephalomyelitis, non infectious inflammatory CNS disease, non suppurative meningoencephalitis, reticulosis etc. For the purpose of this paper the term GME (rightly or wrongly) will be used to describe all non infectious inflammatory CNS disease as it is a widely recognized term. It has a worldwide distribution and may account for up to 25% of ALL CNS disorders in dogs.

GME is recognised most commonly in toy and small breed dogs especially Maltese, miniature poodles and terriers of all kinds (including Staffordshire terriers and Airedales). It can however occur in all breeds including large breeds and crossbred dogs. It is seen most commonly in middle aged dogs (less commonly in dogs

<2 years and >10 years). Both sexes affected although females may outnumber males.

The diagnosis of non infectious CNS inflammatory disease is made on the basis clinical findings and the exclusion of infectious causes -often based on serology, CSF analysis, and brain imaging. In many cases however a tentative diagnosis is made based on best guess considering breed, age, history and clinical signs. Typically animals with CNS inflammatory disease present with an acute onset of multifocal CNS signs (brain or spinal cord) and/or hyperesthesia (cervical or thoracolumbar). Clinical signs include forebrain abnormalities (alterations in mentation, compulsive circling, seizures), and / or caudal fossa abnormalities (ataxia, vestibular disturbance, cranial nerve abnormalities). In many cases it is difficult to make a neuroanatomic diagnosis. However, a more chronic progressive history and in some cases an episodic history is seen and a significant number of dogs present with focal neurologic signs. Animals with meningitis often have severe neck pain, hunched posture and show reluctance to move and a stiff stilted gait. Many small dogs have a history of hiding and yelping or screaming when picked up of for no apparent reason. Poorly localisable spinal pain is common. Not all affected dogs however will show evidence of spinal pain.

Focal spinal cord signs (of any part of the spinal cord but especially cervical) including paresis or paralysis may be seen. An optic neuritis form of GME is often described but is uncommon. Clinical signs can be acute in onset and rapidly progressive or more insidious in onset and slowly progressive over weeks or months. In summary GME can present with any history, any neurologic signs, at any age in any breed!

Attempts to characterise forms of GME as disseminated, focal or optic have been made. This is often difficult antemortem and may or may not be significant with respect to diagnosis, treatment and prognosis.

Generally there are no abnormalities on physical examination or on haematology or biochemistry profile in affected dogs. Pyrexia may be seen but is uncommon.

CSF analysis generally shows mild to moderate pleocytosis with a predominance of mononuclear cells and variable increases in CSF protein. Total WBC count can vary from <10 cells to > 5,000 cells. CSF protein may be normal or up to 4g/L. Neutrophils usually account for less than 50% of cells seen. Macrophages and occasional eosinophils may also be seen. Some dogs (may be more

than 10%) will have a normal CSF. CSF findings may indicate inflammation that is suggestive of GME but other conditions can also cause a similar CSF picture including infectious causes. In most cases CSF analysis does not provide a definitive diagnosis but can be one of the pieces of a puzzle when trying to establish a likely diagnosis in cases of spinal or intracranial disease. CSF analysis will determine whether inflammation is present but only if inflammation involves the meninges, ependymal lining or tissue close to CSF pathways. Non specific CSF abnormalities are commonly seen in vascular, traumatic, degenerative, neoplastic and inflammatory CNS conditions.

Significant risk is associated with the collection of CSF in animals with increased intracranial pressure (ICP) where brain herniation, either of the cerebral hemisphere/s under the tentorium cerebelli or herniation of the cerebellum through the foramen magnum, is a possible sequela. CSF collection is also risky in animals with severe brain disease with or without increased intracranial pressure where changes in cerebral perfusion associated with anaesthesia and lack of normal brain autoregulatory responses may result in further deterioration in neurologic status. Unfortunately these are often the animals where CSF analysis is of most value. Clinical signs associated with increased ICP include obtundation, stupor, panting, headpressing, bradycardia and increased systemic blood pressure. Some animals with increased intracranial pressure will not have any obvious clinical signs.

Damage to neural structures (spinal cord or medulla oblongata) is also a risk with cisternal CSF collection, especially in small animals or in animals with obstruction to CSF flow at the level of the cerebellomedullary cistern. The majority of dogs with GME are small and may be of breeds with cranio- cervical junction abnormalities such as Chiari like malformation.

I do not routinely perform CSF collection in dogs with a high index of suspicion of GME.

Brain imaging may also show abnormalities suggestive of inflammatory disease and MRI is the diagnostic modality of choice in GME. Magnetic Resonance imaging (MRI) is the most sensitive imaging technique in evaluating the brain and spinal cord. There is however no “typical” MRI picture and lesions may be indistinguishable from infectious, vascular or neoplastic disease. Single or multiple lesions may be seen anywhere in the neuroaxis that may be hypointense on T1 weighted images, and hyperintense on T2 weighted and FLAIR images. Contrast enhancement is

variable. Meningeal enhancement may be evident. In some cases no abnormalities are seen. Computed Tomography (CT) is less sensitive especially in evaluating caudal fossa lesions (beam hardening artifact). “Mass effect” –deviation of the falx or disruption of normal brain anatomy may or may not be seen in either CT or MRI.

A definitive diagnosis of GME can only be made on histopathology which can be achieved by brain biopsy or brain examination- which is obviously difficult ante mortem! Microscopically GME is characterized by perivascular lymphocytic and /or macrophage cuffing. These lesions may coalesce into macroscopic granulomas.

A tentative diagnosis of GME is often made by exclusion of other causes (serology/ culture of CSF in some circumstances) and in many cases on response to treatment. To rule out infectious causes of meningoencephalitis serum Cryptococcal antigen titre (LCAT), serum toxoplasma gondii and neospora caninum antibody titres (and in some instances CSF titres) may be necessary. CSF culture is often negative even in cases of infection.

In animals with severe neurologic signs the benefits of diagnostic tests especially CSF analysis need to be weighed against the risks of the procedure.

The cause of GME is not known- autoimmunity is most likely and GME may represent a T cell mediated hypersensitivity.

The prognosis is difficult to predict. GME can be an acute, rapidly progressive and fatal disease despite treatment but many cases of presumed GME have responded well to treatment and remained in remission for months to years. Most literature on GME gives a poor to hopeless prognosis associated with this disease but in practice many apparent GME cases do well. It is a histologic diagnosis and the literature is largely based on animals with a confirmed diagnosis (ie are dead). **Prognosis cannot be based on the severity of clinical signs on presentation nor on the degree of abnormality on CSF analysis or brain imaging.**

Immunosuppressive doses of corticosteroids (primarily prednisolone) remain the mainstay of treatment. In many cases (for financial and/ or risk of further diagnostic testing) empiric treatment is indicated without a more definitive diagnosis. Starting

dose of prednisolone is 1-2mg/kg q12 hours. Small dogs (<10kg) should be given 2mg /kg q12 hours. Dogs <2.5 kg should be treated as a 2.5 kg dog and those <5kg as a 5kg dog. Larger dogs (>40kg) should be treated as a 40kg dog and I would generally give no more than 40mg/kg q12 hours for extended periods of time. Affected dogs may take several days to show any response to corticosteroid therapy.

The dose of prednisolone is tapered over at least 6 months depending on clinical response. Initially the dose should be reduced after 2-4 weeks. If remission is achieved animals should be maintained on prednisolone (0.5-1mg/kg every other day or 2-3x a week) for 1-2 years or life. Whether affected animals are "cured" is difficult to determine. If a dog is free of neurologic signs for > 6 months and managed with prednisolone at a low dose 2-3 x a week treatment may be discontinued. However corticosteroid side effects especially in larger breed dogs are a significant problem in the long term. Long term high dose corticosteroids cause iatrogenic hyperadrenocorticism with significant muscle wasting and calcinosis cutis. Treatment also predisposes to gastrointestinal ulceration, pancreatitis, diabetes mellitus, infection (especially UTI) ligamentous and tendon injury. Small dogs often tolerate high dose therapy well, however in dogs which show a recurrence of neurologic signs with corticosteroid therapy or require high levels of corticosteroids (> 1mg/kg) for long periods to alleviate neurologic signs or have significant corticosteroid side effects other immunosuppressive drugs should be considered. In larger breed dogs adjunctive therapy with other drugs should be considered early (within months) as high dose corticosteroid treatment is often poorly tolerated. The use of other immunosuppressive drugs may enable a reduction in the dose of prednisolone given, however for most animals treatment with some level of prednisolone is also necessary.

Azothiaprime (Imuran) is immunosuppressive and acts to inhibit T cell function. It does not cross the blood brain barrier in normal dogs. Although it may be useful in the treatment of corticosteroid responsive meningitis especially in young large breed dogs, in my hands it does not seem to be helpful in dogs with GME. Having said this, other clinicians have recommended treating with imuran and have had some success using azothiaprime in combination with prednisolone allowing for a reduction in prednisolone dose. It is relatively free of side effects with myelosuppression the main concern at higher doses. Recommended dose is 0.5-1.0mg/kg q48 hours. 2mg/kg q24 hours for first 5-7 days may be used.

Cytosine Arabinoside (Cytarabine, Ara-C) is a drug that has been used as an antineoplastic agent in dogs and humans and has been used to treat CNS lymphoma. Its mechanism of action is not known. Due to its ability to cross the blood brain barrier and its immunosuppressive effects cytarabine was proposed as a potential treatment for GME approximately 6 years ago. Most authors recommend treatment with 50mg/m² by subcutaneous injection twice a day for 2 consecutive days with this cycle repeated every 3 weeks. This dose is lower than doses generally used as part of chemotherapeutic protocols for neoplasia. Side effects associated with Cytarabine are few. Myelosuppression (seen generally 10-14 days post initial treatment) is reported but is generally not a clinical problem. CBC should be monitored periodically but is not necessary at every cycle. Vomiting, diarrhea and/or inappetence may occur after treatment. Cytarabine is inexpensive (when purchased in 1ml vials) and animals can be treated on an outpatient basis however gloves should be worn when administering this drug and handling/disposing of urine and faeces. Cytarabine is used in conjunction with prednisolone and I usually reduce the prednisolone dose incrementally after each 2 cycles of cytarabine if an animal's neurologic status is stable. Cytarabine can be used indefinitely.

Leflunomide (Arava) is an immunomodulatory drug used in humans primarily in the treatment of rheumatoid arthritis. It has been used in dogs in conjunction initially with corticosteroids and as "stand alone" agent in dogs with unmanageable corticosteroid side effects with reported success. The dose given is 2mg/kg once a day initially. In my hands treated animals have relapsed or not improved. It is not associated with any significant side effects and is given orally. It can also be given with prednisolone.

Cyclosporin has also been proposed as a treatment for GME as it has been suggested that GME is a T-cell mediated autoimmune disease. Cyclosporin is a potent immunosuppressive drug and suppresses T-cell mediated immune responses. The blood brain permeability of cyclosporine however is poor in normal animals. However GME is a perivascular disease and the blood brain barrier is likely to be disrupted and it is proposed that cyclosporin concentration is probably higher in affected areas of the CNS. It is also suggested that T-cell response is initiated in the peripheral lymphoid organs in autoimmune disease and therefore cyclosporins effect does not rely on it crossing the blood brain barrier to suppress the immune response to the CNS. One author (Adamo) recommends cyclosporine monotherapy at a starting dose of 6mg/kg q12 hours with a blood cyclosporine trough level target of 200-400ng/ml. The trough level should be tested in 5-7 days and

reevaluated in 1 month and every 4-6 months thereafter. Cyclosporin can be given in combination with prednisolone. Cyclosporin therapy is expensive especially in larger dogs and concurrent ketaconazole treatment has been used to decrease the clearance of cyclosporine by inhibition of microsomal enzyme activity. Doses recommended are cyclosporine 5mg/kg/day PO and ketoconazole 8mg/kg/day PO. This protocol is not recommended in dogs with elevation of liver enzymes or other medical conditions that may exacerbate hepatic insufficiency. Monitoring is as for cyclosporin therapy alone. Side effects include hair loss/shedding, gingival hyperplasia and hypertrichosis. Signs of toxicity are vomiting, diarrhea and anorexia. Myelosuppression is not generally a concern.

I have limited experience with this drug and it has not been helpful in treated dogs (2) that have failed on treatment with prednisolone and cytarabine.

Procarbazine is an antineoplastic drug that is lipid soluble and readily crosses the blood brain barrier and used predominantly in human medicine to treat lymphoma. A dose of 25-50 mg/m² /day has been recommended. This drug requires reformulating into an oil based solution by a pharmacist (as the powder is toxic) in small patients as it is generally available as 50mg capsules only. Procarbazine is associated with a high incidence of side effects including myelosuppression (30%), haemorrhagic gastroenteritis (15%), nausea, vomiting and hepatic dysfunction. CBC should be monitored weekly for the first month then monthly. Gloves should be used when handling this drug (and urine and faeces). I have no experience with this drug and its efficacy has not been proven. Its side effects and availability also limit its use.

Lomustine (CCNU) is an antineoplastic alkylating agent in the nitrosurea class that is highly lipid soluble and crosses the blood brain barrier. It is used to treat lymphoma and some brain tumours in dogs. The treatment dose for brain tumours is 60mg/m² every 6 weeks for 6 months. The doses used to treat lymphoma are higher. The dose used to treat GME is relatively arbitrary but high doses are not recommended. Treatment with lomustine is associated with significant and in some cases life threatening myelosuppression, gastrointestinal ulceration and hepatotoxicosis. Side effects increase with increased dose but may also be seen after an initial, relatively low dose. Sepsis is a significant risk with myelosuppression. Toxicity is not predictable and I have not recommended its use routinely as a first choice treatment.

Animals with seizures should also be treated with an anticonvulsant.

Affected animals should not be vaccinated unless absolutely necessary. Relapse of clinical signs may be seen after vaccination. A low fat diet is also recommended.

Response to therapy is generally assessed on improvement or resolution of clinical signs. Repeating CSF analysis is not generally recommended as the degree of abnormality (or lack thereof) on CSF analysis has not correlated well with the severity of CNS inflammation.

In my experience at least 60% of dogs with presumed GME or non infectious corticosteroid responsive meningoencephalitis do well with treatment with corticosteroids alone and many are eventually tapered off treatment with no recurrence. Recurrence however may be seen days, weeks, months or years after initial onset of clinical signs. Animals that have persistent neurologic signs despite high levels of corticosteroids and/or the prednisolone dose cannot be reduced to < 2mg/kg/day without relapse after several months of therapy, have a poorer long term prognosis.

Of animals that require high levels of corticosteroids for long periods to reduce their neurologic abnormalities the addition of cytarabine has helped in reducing the prednisolone dose required and a reasonable quality of life may be seen for months or >1 year.

Other idiopathic meningoencephalitides have been described in several small breeds including pug dog encephalitis, necrotising encephalitis of Yorkshire terriers (necrotizing leucoencephalitis), Chihuahuas and Maltese (necrotizing meningoencephalitis). Necrotising encephalitis may also be seen in other toy breeds. The histopathologic findings show extensive inflammation and predominantly cerebrocortical necrosis. The pattern of necrosis and cavitation of the brain parenchyma and presence or absence of meningeal lesions is often characteristic of these breed associated inflammatory diseases and the MRI findings closely mirror the histopathologic lesions at necropsy. The prognosis for all is very guarded. Treatment is as for GME although the response to treatment is often poorer.

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Insulin Preparations For Diabetic Dogs And Cats – What Is New, What Is Still Available, And How To Best Use Them

Dr Linda Fleeman

An enormous variety of human insulin preparations are available in Australia and New Zealand, as well as one insulin preparation registered specifically for use in dogs and cats. All products are potentially efficacious for the treatment of diabetes mellitus in small animal patients although there is limited veterinary information on most of the recently released human products. As improved therapeutic protocols are developed for the management of human diabetes, new products are continually being developed while others are withdrawn. The current trend in human medicine is towards long-acting, 'peakless' insulin preparations that aim to provide continuous basal insulin supplementation, and which are typically combined with administration at meal times of a rapid-onset, short-acting insulin preparation. This has resulted in a decline in the market for intermediate-acting insulin products and the pre-mixed combinations of short- and intermediate-acting insulin. Unfortunately, it is these products that are most commonly used for the management of canine and feline diabetes and veterinarians must now adapt to the withdrawal of several familiar insulin preparations.

WHICH INSULIN PREPARATIONS HAVE BEEN WITHDRAWN?

Monotard (produced by Novo Nordisk) and Humulin L (produced by Eli Lilly) were both 100 units/mL preparations of lente insulin marketed for human diabetics that have recently been discontinued. Ultratard (Novo Nordisk) and Humulin U (Eli Lilly) were longer-acting ultralente preparations that were also discontinued. The convenient 10 mL vials of Mixtard 30/70 (Novo Nordisk), which is a 100 units/mL pre-mixed combination of 30% short-acting regular insulin and 70% intermediate-acting isophane (NPH) insulin, are no longer available in Australia, but can still be obtained in New Zealand.

IDEXX Pharmaceuticals have recently announced their intention to withdraw PZI VET, which is a 40 units/mL bovine/porcine preparation of protomine zinc insulin registered in several countries for veterinary use. Although PZI VET has not been locally available, it is a popular veterinary product elsewhere in the world and its loss highlights the practical problems often associated with production of animal sourced insulin.

WHICH INSULIN PREPARATIONS ARE STILL AVAILABLE?

Caninsulin (produced by Intervet)

The only lente insulin preparation now available in Australia and New Zealand is Caninsulin, which is a 40 units/mL porcine insulin zinc suspension specifically registered for veterinary use. There is very strong evidence that this insulin product is effective for the treatment of diabetes mellitus in both dogs¹ and cats². Lente insulin has an intermediate duration of action and is a combination of 30% semilente insulin, which has a short duration of action, and 70% ultralente insulin, which has a long duration of action. This combination results in a relatively predictable and rapidly obtained peak effect. The average duration of action of Caninsulin in dogs is 16 hours resulting in significant lowering of blood glucose concentration in the majority for 12 hours or less^{3,4}. It is particularly suited to a twice-daily dosing regimen in diabetic dogs because the meal can be fed soon after the insulin injection. The average duration of Caninsulin action in cats is much shorter⁵ and lowering of blood glucose is usually achieved for less than 12 hours. The more dilute 40 units/mL Caninsulin preparation is advantageous for cats and small dogs, which might require a total insulin dose of only 1 or 2 units.

For diabetic dogs and cats that were stabilised on Monotard or Humulin L, a direct dose-for-dose swap can be made if changing to Caninsulin. The animal should be monitored closely after the changeover and appropriate dose adjustment made to ensure optimal glycaemic control. Care must be taken to ensure that owners understand that Caninsulin is a more dilute preparation and so a larger volume must be administered to provide the same dose. Dosing can be made simpler by prescribing specific U-40 syringes for Caninsulin.

Mixtard 30/70 (produced by Novo Nordisk)

In Australia, this product is still available in 3 mL pen-fill cartridges that can be purchased in packs of five. In New Zealand, both 10 mL and 3 mL Mixtard 30/70 products are still available. This 100 units/mL pre-mixed combination of 30% regular and 70% NPH insulin has a similar action to lente insulin and so is also suited to a twice-daily dosing regimen in diabetic dogs where the meals are fed soon after the insulin injections. Similar to Caninsulin, a direct dose-to-dose swap can be made if changing a patient previously controlled with Monotard or Humulin L to Mixtard 30/70. The pen-fill cartridges are used in insulin dosing pens that can administer insulin doses in either 0.5 or 1 unit increments, and so provide a practical option for cats and small dogs that require small doses of insulin or for owners who have difficulty measuring and administering insulin doses using a syringe.

Humulin 30/70 (produced by Eli Lilly)

Both 10 mL vials and 3 mL pen-fill cartridges of Humulin 30/70 are still and will continue to be available. This insulin preparation is also a 100 units/mL pre-mixed combination of 30% regular and 70% NPH insulin with the same advantages and indications as Mixtard 30/70.

Protophane (produced by Novo Nordisk) and Humulin NPH (produced by Eli Lilly)

Protophane and Humulin NPH are both 100% isophane (NPH) insulin at 100 units/mL and have an intermediate duration of action. These products are effective for the treatment of diabetes in dogs, but the ideal time for feeding the meal is several hours after the insulin injection, which is often inconvenient for owners.

WHAT ABOUT THE NEWER INSULIN PREPARATIONS?

Lantus (produced by Sanofi Aventis)

Lantus is a 100 units/mL preparation of glargine insulin, which is a long-acting synthetic insulin analogue developed for the human diabetic market to provide continuous basal insulin concentrations that inhibit hepatic glucose production. The therapeutic aim is to mimic the physiological pattern of insulin secretion of healthy subjects, and the basal insulin levels provided by these products are supplemented at meal times by administration of ultra-short acting insulin preparations that act during the postprandial period⁶.

Glargine insulin is efficacious for the treatment of diabetes in cats and initial results indicate that it might be a better choice than lente insulin⁷. When changing a stabilised diabetic cat to glargine insulin, it is recommended that the same guidelines are followed as are used when commencing glargine therapy in a newly-diagnosed cat⁸.

Pre-filled 3 mL insulin dosing pens are available and allow administration of doses in 1 unit increments. Lantus is also available in 3 mL pen-fill cartridges and 10 mL vials. Many owners appear to be able to measure doses in 0.5 unit increments if they use a 0.3 mL insulin syringe. However it is worth noting that insulin dosing pens are much more accurate and precise than insulin syringes for small doses. When administering a dose of 1 unit of glargine insulin using the dosing pens that are available for Lantus, the mean dose delivered using the AutoPen (3mL cartridges) is 0.93 units (range: 0.63-1.20 units) and for the SolarStar (pre-filled pen) is 1.02 units (range: 0.60-1.40 units). In comparison, a study evaluating the accuracy and precision of insulin dosing by paediatric nurses using 0.3 mL or 0.5 mL insulin syringes found that the mean $\pm$ SD dose delivered when intending to administer 1 unit was 1.64 $\pm$ 0.38 (range: 0.65-2.80 units)⁹. Importantly, it can be seen that most syringe-measured doses exceed the intended dose.

In contrast to cats, information regarding the use of glargine insulin in diabetic dogs is limited, and initial pharmacological assessment in healthy dogs found that glargine administration resulted in an unpredictable serum insulin concentration response and failed to produce a significant glucose-lowering effect in 2 of 9 dogs after a single injection¹⁰. For diabetic dogs, it is important to use an insulin preparation that has a predictable and reliable glucose-lowering effect. This is because it is crucial that the period of maximal insulin action coincides with the postprandial period if clinical signs are to be controlled with minimal risk of

hypoglycaemia. Generally, the longer the duration of action of an insulin preparation, the greater the variability in response between dogs receiving the same dose and the less predictable the period of maximal insulin action. Until there is further evaluation of the efficacy of glargine insulin for the treatment of diabetes in dogs, it is not recommended that it is used for initial therapy.

Levemir (produced by Novo Nordisk)

Levemir is a 100 units/mL preparation of detemir insulin, which is another long-acting synthetic insulin analogue that provides continuous basal insulin supplementation for human diabetics. There is little specific information currently available on its use in the treatment of diabetic cats and dogs.

NovoRapid (produced by Novo Nordisk) and Humalog (produced by Eli Lilly)

The ultra-short acting insulin preparations available in Australia are NovoRapid (100 units/mL insulin aspart) and Humalog (100 units/mL insulin lispro). There is currently no specific indication for their use in the long-term management of canine or feline diabetes mellitus.

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Seizure Disorders And Anticonvulsant Medication In Dogs And Cats

Dr Georgina Child

Seizures are a relatively common disorder in companion animals. More than one in one hundred people have a seizure disorder and although no studies have been done to assess the incidence of seizures in dogs it is probably just as high (estimated at 1-5% of all dogs). A seizure is a transitory disturbance of brain function. Seizures may be generalised due to a generalised brain disturbance or seizures may be partial arising from a specific area of the brain. Generalised seizures (grand mal type) are characterised by loss of consciousness, muscle rigidity, involuntary running or paddling movements, salivation, urination and/or defecation. Although generalised seizures are distressing to see, they are usually brief lasting less than 2 minutes. Generalised seizures may be preceded by an aura or period where dogs seem anxious, seek owners or are hyper excitable. Partial seizures vary in nature depending on the area of brain from which they arise but possible abnormalities seen include involuntary movements, abnormal behaviour, and gastrointestinal signs but animals remain conscious, although mentation may be altered (staring, aggressive, or “not all there”). Partial seizures may last for a longer period of time than generalised seizures. Absence or petit mal seizures -blank staring and reduced muscle tone seen in people- are rarely recognised in dogs. The post ictal phase is the period immediately after either a generalised or partial seizure. In this phase animals often seem exhausted and sleep or may seem restless, pace constantly, walk in circles, seem disoriented and/or staggering. Dogs may seem blind or even demented and vocal. They are often thirsty or hungry. The post ictal phase may last from minutes to days and the length may not bear any relationship to the length of the seizure episode. Seizures may occur in clusters with more than one seizure seen in a short period of time.

Seizures may be the result of abnormalities outside of the brain (extra cranial) or due to a primary brain abnormality (intracranial). Reactive seizures are due to extra cranial causes such as metabolic disturbance or toxic insult. Metabolic disturbances that can cause seizures include low blood glucose,

low blood calcium, high blood potassium, liver disease, kidney failure, thiamine deficiency and hyperlipoproteinemia. Lead, snail bait (OP and carbamate), strychnine, 1080 and brufen (yesterday, today and tomorrow) poisoning can cause seizures in dogs.

Symptomatic seizures occur as a result of a structural brain abnormality. Brain abnormalities that can cause seizures include congenital brain anomaly (eg hydrocephalus), head trauma, encephalitis (brain inflammation), brain tumour or cerebrovascular accident (stroke). Seizures may not be seen for weeks, months or years after brain damage occurs. In some instances the underlying cause of the seizures may progress and other neurologic abnormalities are seen (tumour, encephalitis) but in other cases the structural brain abnormality may be static (prior head injury, vascular accident) and recurrent seizures (epilepsy) the only abnormality seen. This form of epilepsy has been called acquired or symptomatic epilepsy. Partial or generalised seizures may be seen in acquired epilepsy.

Idiopathic epilepsy is a seizure disorder where no underlying cause can be established. It is the most common cause of seizures in dogs. It may have a genetic (inherited basis) in many cases. This form of epilepsy is better called genetic or primary epilepsy. However some cases of idiopathic epilepsy may have a structural cause (for example birth injury) which cannot be confirmed by routine examination as seizures may not be seen for years after a brain injury. This form of epilepsy has been termed cryptogenic (from the Greek meaning hidden). Idiopathic epilepsy presumed due to genetic abnormality is characterised by generalised seizures. However partial seizure disorders have been recognised in related dogs and some partial seizure disorders may in fact be inherited.

Epilepsy has been shown to be inherited in beagles. Data suggests that it is also inherited in German shepherd dogs, Keeshonds, Belgian (Tervuren) shepherd dogs, dachshunds, Hungarian Vizslas, English springer spaniels, Irish Wolfhounds and collie dogs. Several breeds have been reported to have a high incidence of seizure disorders including golden retrievers, German shepherd dogs, Irish setters, Saint Bernard, American Cocker Spaniels, wirehaired fox terriers, Alaskan Malamutes, Siberian Huskies, Welsh springer spaniels, Labrador retrievers, miniature schnauzers, mastiffs, Border collies, Boxers, CKCs and poodles. Epilepsy probably has an inherited basis in these breeds.

Epilepsy may occur in any breed including cross bred dogs and the incidence of epilepsy seems to be constant across breed and cross breed boundaries. One study suggests the high incidence of seizure disorders in certain breeds may reflect the popularity of these breeds. In my practice boxers, Border collies, Dalmatians and Maltese terriers are over represented but all are currently popular breeds as family pets. Male dogs have a higher incidence idiopathic epilepsy than females. Acquired or symptomatic epilepsy may be seen in any breed dog of either sex. An increased frequency of seizures may be seen in females during oestrus or pregnancy and it is not uncommon for females to have their first seizure when in season.

Idiopathic(primary) epilepsy is most often recognised in dogs between 1 and 3 years of age however dogs may have their first seizure before 6 months or older than 3 years. Acquired epilepsy and reactive seizures may be seen in dogs of any age. Dogs that have their first seizure at less than 5 years of age are most likely to have idiopathic(primary) epilepsy. Dogs that have their first seizure at greater than 7 years of age are much more likely (50%) to have acquired cause which is more likely to have a progressive aetiology (for example brain tumour).

Genetic or inherited epilepsy is rare in cats but does occur. Acquired epilepsy (eg secondary to head trauma) is seen and cats may have a higher incidence of encephalitis and cerebrovascular abnormalities resulting in seizures than dogs.

Dogs with a normal neurologic exam and recurrent seizures that are 5 years of age or younger and no metabolic abnormalities are most likely to have primary epilepsy(if generalised seizures) or acquired epilepsy (if partial seizures). No further diagnostic tests are usually recommended unless the dog goes on to show neurologic abnormalities between seizures suggesting a progressive aetiology. **In cats of any age**, with no neurologic abnormalities on neurologic exam, infectious causes of seizures should still be considered and investigation for FIP, cryptococcal and toxoplasma infection may be warranted.

Dogs that are 5-7 years of age when seizures are first seen with a normal neurologic exam and no metabolic abnormalities are most likely to have an acquired cause. Some of these dogs will have a progressive cause such as brain tumour. These dogs should be monitored closely and if seizures increase in frequency or more importantly if neurologic signs are seen between seizures further diagnostic tests should be considered.

Dogs that are 7 years of age or older when seizures are first seen with a normal neurologic exam and no metabolic abnormalities have a 50% probability of an underlying progressive intracranial disease such as a tumour . If metabolic causes are ruled out brain imaging should be considered.

In cats older than 5 years of age (and more especially older than 10 years) intracranial tumour and cerebrovascular disease secondary to hypertension (renal disease, hyperthyroidism) should also be considered.

If an underlying cause of seizures is found specific treatment should be given.

If idiopathic (primary or acquired) epilepsy is diagnosed the decision on whether or not to start treatment with anticonvulsant medication depends on seizure frequency and severity. Animals that seizure infrequently (less than 1 seizure every 4-6 weeks) generally do not require medication unless seizures are long, are accompanied by intolerable behaviour changes, or seizures are distressing to the owner. **Dogs that seizure more frequently than 1 seizure a month and/ or have seizures in clusters (more than 2 seizures in 24 hours) and/or have ever had an episode of status epilepticus (continuous seizuring) and/or have prolonged seizures (> 5 mins) should be treated with anti convulsant medication.**

There is evidence to suggest the more seizures an animal has the more likely it is to seizure again as if the brain becomes ‘wired’ to seizure more easily. Early institution of anticonvulsant therapy may result in better seizure control although starting therapy after a single seizure may result in unnecessary treatment of dogs that would have seized very infrequently. Seizures are generally not life threatening however misadventure associated with seizure may result in death (falls in swimming pool and drownings) and status epilepticus (state of continuous seizures or repeated seizuring without recovery between seizures) is a medical emergency. Repeated and frequent seizures is associated with neuronal damage- both acutely and chronically.

Anticonvulsant medication is a long term and often lifetime commitment. Medication needs to be given every day at regular intervals. All anticonvulsant medication is associated with drug related side effects-these effects may be dose related but may also vary in severity from animal to animal given the same drugs.

Epilepsy is not a curable disease – at best it is a manageable disorder. The “success” of treatment is in most cases not the abolition of seizure activity. Controlling seizures completely is an unrealistic expectation . “Therapeutic control” will vary from animal to animal and may be measured by reduction in frequency and /or severity of seizures and/ or the minimisation of adverse drug effects. Up to 30 % of animals with epilepsy will remain “refractory” to anti convulsant medication despite high levels of medication and often combination drug therapy.

There is no advantage to combination therapy over monotherapy in the initial treatment of epilepsy. Prediction of the likely success of treatment is difficult . Several factors may be associated with poorer seizure control despite appropriate medication including a younger age of onset of recurrent seizures (especially < 1year), the development of a cluster pattern of seizures (especially early), and episodes of status epilepticus.

The most effective anticonvulsant in dogs is still **phenobarbitone**.

Phenobarbitone is a non selective CNS depressant with a long duration of action .The mechanism of action is unknown (may enhance or mimic synaptic action of GABA) but believed to be due to depression of monosynaptic and polysynaptic transmission and increasing the threshold for electrical stimulation of the motor cortex. Anticonvulsant activity is seen at sub hypnotic doses. Starting dose of phenobarbitone is 2-4mg/kg q12hours (dogs) and 2mg/kg q12 hours for cats. Animals may be sedated and ataxic for first 10-14 days but generally become tolerant to the sedative effects of the drug. If animals are excessively sedated the dose should be halved and then increased again in 2 weeks. Occasionally dogs will become hyperactive and excessively vocal- this effect also generally subsides with continued treatment and increased dose. A serum phenobarbitone level of >150umol/L may be required to control seizures. A phenobarbitone level of >170umol/L is more likely to be hepatotoxic. Phenobarb dose given should be determined by serum level as individual dose requirements vary considerably. **The therapeutic level of a drug is a guide only- it is not an indication the drug will be effective if the serum level is in any part of the “therapeutic range” – some dogs will be poorly controlled at a drug level at the lower end on the therapeutic range and better controlled with a higher blood level.** The value of the therapeutic range reference values as given by laboratories is really only in the upper limit. If an animal is not showing continued seizures then it does not really matter what the serum level is or if it is “too low”. If an animal is still seizing frequently then the current level of medication is not working even if the drug level is in the therapeutic range and an

increased drug level may result in better seizure control. The upper end of the therapeutic range is helpful only in determining likelihood of hepatotoxicity and in limiting any further increases in dose. Most dogs will not show high serum drug levels until the dose given is 8-10mg/kg q12 hours (smaller dogs often higher levels, large breed dogs may be lower). Persistent adverse side effects such as excessive sedation (to which a tolerance does not develop) is generally the limiting factor to increasing the amount of phenobarbitone given and may occur at any serum level – usually above 120umol/L. Routine monitoring of serum phenobarbitone levels is generally not necessary unless animals are on high levels of phenobarbitone, adverse side effects are persistent (ataxia, paraparesis, excessive sedation) or hepatotoxicity is suspected. Routine monitoring of liver parameters is important and should be performed yearly in animals on low to mid range phenobarbitone doses and 6 monthly on animals on high levels of phenobarbitone or those with evidence of liver abnormality. Most animals receiving phenobarbitone will have elevated alkaline phosphatase due to the induction of hepatic microsomal enzymes – up to 1,000 U/L. Mild elevations in ALT are also common. This is not necessarily evidence of significant liver disease. However increasing levels of liver enzymes should be monitored and liver function tests (eg pre and post prandial bile acids) performed if concerns. Phenobarbitone levels should be measured from a blood sample collected in a serum tube without a clot activator. Blood samples should be drawn within several hours of the next scheduled dose. Samples can be drawn at any time of day but if trends are to be compared then samples should be drawn at the same time of day with respect to dosing in individual animals. The animal should have received its normal medication on time for at least several days prior to sampling. If medication has not been given as usual or additional medication has been given the serum level will not be a valid representation of “normal” blood level. Due to the long elimination half-life any changes in phenobarbitone dose will take 2-3 weeks to reach a steady serum level. Maximum serum levels are reached in 4-8 hours. The time to reach steady state serum levels may be decreased if 2x the calculated maintenance dose (or more) is given for several days- this “loading dose” however may be associated with significant sedation. A loading dose is used in animals that present for an acute onset of seizures and require hospitalisation (not due to metabolic abnormality, regardless of the cause).

Common side effects of phenobarbitone include polydipsia, polyuria, polyphagia and sedation. Polyphagia is often associated with weight gain and of major concern to pet owners. Garbage intoxication, oesophageal and gastric foreign bodies and coprophagia are possible sequelae. Behaviour abnormalities

including increased vocalisation and restlessness may be due to food seeking behaviour or a psychogenic drug effect.

Blood dyscrasias(including neutropenia and anaemia) and superficial necrolytic dermatitis have also been reported with phenobarbitone therapy- these are very uncommon and may be seen in dogs soon after institution of therapy or after years of therapy. These problems usually resolve with cessation of therapy.

Phenobarbitone can be given with or without food but must be given at a 12 hour interval. Sudden discontinuation of phenobarbitone may result in “withdrawal” seizures.

Phenobarbitone may decrease the effectiveness of other drugs given concurrently eg ketaconazole. Chloramphenicol increases serum phenobarbitone levels. Check MIMs for any potential drug interactions.

Primidone (Mysoline) is metabolised primarily into phenobarbitone. Metabolites primidone, Phenylethylmalonamide-PEMA and phenobarbitone all have anticonvulsant activity however it is estimated 80-85% of this activity is due to phenobarbitone and in the majority of animals provides no better seizure control than the equivalent serum level of phenobarbitone. It may be associated with more severe sedation and is associated with greater likelihood of hepatic toxicity and behavioural abnormalities. A very occasional dog has better control with primidone than phenobarbitone however the incidence of adverse effects and increased expense generally does not warrant its use.

Potassium bromide (20-30mg /kg q24 hours as single or divided doses) is useful as an add on anticonvulsant drug if seizures are not well controlled with phenobarbitone alone or as a single drug if the side effects of phenobarbitone are not tolerated or other factors preclude the use of phenobarbitone. The mechanism of action of bromide salts is not known. Potassium bromide is the Br salt most commonly used as an anticonvulsant. KBr must be given with food (a reasonable amount). The common salt content (NaCl) of the food given should be kept constant . KBr has a half life in dogs of 21-29 days and will take 16 weeks to reach a steady serum level. A loading dose of KBr may be given to achieve higher serum levels more quickly however this is often associated with marked sedation and gastrointestinal side effects (vomiting/diarrhea). Marked sedation and GIT effects may also be

seen on initiation of Br at maintenance doses- if this occurs stop medication for 24 hours and reinstitute at a lower dose. KBr may cause pulmonary disease (allergic pneumonitis which can be fatal) in cats and although it is often an effective anticonvulsant drug it should not be given to cats. Bromide levels should be monitored in animals receiving this drug. There is no point however in monitoring Br levels in dogs after treatment has started for at least 4 months unless toxicity is suspected. Bromide levels >20mmol/L in animals on combination therapy may cause clinical signs of toxicity. Toxicity is characterised by ataxia-often cerebellar in character, abnormal behaviour and abnormal facial movements. Sedation may or may not be evident). In animals where KBr has been added to phenobarbitone and seizure frequency is significantly reduced the dose of phenobarbitone may be reduced after 6 months of combination therapy. Phenobarbitone should always be reduced in a stepwise fashion (7.5mg per dose) every 2-4 weeks. The same phenobarbitone dose should always be given am and pm . Serum Bromide levels in my experience may change (up or down) in animals that have been receiving medication for extended periods of time with previously very stable serum Br levels. The sodium chloride content of diet will affect the absorption of KBr (Cl⁻ competes with Br⁻ for absorption). Changes in Br level may be associated with changes in food, gastrointestinal disease, change in Br formulation (or possibly poor mixing/measuring of doses of oral solutions), consumption of salt water in dogs that swim frequently. In many there is no apparent cause. I see Br toxicity more frequently than phenobarbitone toxicity. If signs of toxicity are seen the dose should be reduced (can stop administration for 24-48 hours). KBr does not cause hepatotoxicity, it is not metabolised and is excreted by the kidney. Renal disease may result in impaired excretion and elevation in Br levels. Skin rashes and pruritis are associated with bromide therapy in humans and may be seen in dogs on KBr at any dose. Be aware that some biochemical analysis techniques will read Br⁻ as Cl⁻.

More recent studies have shown increased fasting triglyceride levels in dogs receiving phenobarbitone or phenobarbitone and KBr. Fasting serum triglyceride levels increased with higher body condition score. Phenobarbitone is known to cause polyphagia and KBr anecdotely also causes polyphagia. This increase in triglyceride level was not correlated with increasing drug doses. Although treatment with KBr has been implicated for many years as a possible cause of pancreatitis, dogs receiving phenobarbitone alone or in combination therapy with KBr are also at risk of developing pancreatitis. Pancreatitis may be seen in dogs of a younger age with no other risk factors than is often associated with this disease in the non anticonvulsant treated population. An increased fasting triglyceride level which may be seen in dogs on

anticonvulsant therapy may result in this increased risk of pancreatitis. Animals on anticonvulsant therapy should be provided with a low fat diet and encouraged to exercise to maintain an ideal body weight. Addition of Omega 3 and Omega 6 supplement may be useful. Weight gain and polyphagia are the 2 of the leading complaints of owners of dogs on anticonvulsant medication.

Phenobarbitone is associated with low total thyroxine and free T4 levels in dogs without other evidence of hypothyroidism. Serum TSH levels are not changed significantly in association with phenobarbitone administration. Br treatment does not appear to be associated with significant changes in Total or free T4 concentrations.

Side effects associated with anticonvulsant drugs may be seen with higher doses and in many cases the medication induced complications have to be weighed against the benefits of treatment.

Treatment may fail for several reasons including improper administration (forgetting doses, dog spitting tablets out), gastrointestinal upset preventing drug absorption and interactions with other drugs (phenobarbitone).

Oestrus may cause an increase in seizure frequency.

Many of the anticonvulsants that are used to treat human epilepsy are not effective in dogs and cats for example phenytoin in dogs, sodium valproate (Epilim) or are toxic (lamotrigine). In animals with continued frequent seizure activity that are not able to be managed on phenobarbitone and/or KBr newer anticonvulsants that have shown efficacy in the treatment of seizure disorders in humans such as gabapentin (Neurontin and generic) and levetiracetam (Keppra) may be useful in reducing the frequency of seizures. Comprehensive pharmacologic studies (and/or assessment of their effectiveness) have not been done in animals and both are relatively expensive and require 3-4x a day dosing. These drugs are used as add on drugs (to phenobarbitone and KBr) in most cases. The doses given are empiric and based on trial and error-with the upper limit determined by side effects (predominantly sedation and /or ataxia).

Gabapentin is a synthetic analogue of the inhibitory neurotransmitter GABA its mechanism of action is not known. It is metabolised by the liver and kidney. The initial starting dose is generally recommended as 10-15mg/kg q8 hours but this can be increased (doubled or tripled). It is apparently safe (no metabolic side effects) however sedation is commonly seen especially at

higher doses (additive with phenobarbitone and KBr) and has not been useful in my hands in reducing seizure frequency in animals with refractory epilepsy over and above control achieved with phenobarbitone and KBr. Gabapentin is primarily used in humans to treat partial and complex partial seizures. Gabapentin is apparently safe to use in cats but there is little information on its usefulness as an anticonvulsant. Liquid forms of gabapentin contain xylitol which can be toxic and should not be used in dogs or cats. 100mg capsules can be reformulated into smaller doses for small animals.

Levetiracetam (Keppra) is a newer human anticonvulsant used to treat generalised and partial seizures. Its mechanism of action is unknown and is not metabolised by the liver and excreted essentially unchanged in the urine. It has a half life of 4 hours in the dog. The initial recommended dose is 20mg/kg q8 hours however this can be increased (doubled). Sedation and ataxia are common side effects and increase with increased dose. It is not associated with other known side effects. My experience in using levetiracetam in dogs with refractory cluster seizures that have not been adequately controlled with phenobarbitone and KBr is that a reduction in frequency is often seen for 4-6 months then seizure frequency increases again.

Levetiracetam can also be safely given in cats at the same dose and in my experience seizure frequency is often reduced however increased seizure frequency is often seen again after approx 6 months. Three times a day dosing is difficult for many owners and owner compliance is often poor.

There are no “therapeutic levels” determined in animals and monitoring drug levels is not recommended at this time.

Other drugs such as felbamate and zonisamide and more recently Lyrica are not currently available in Australia. Topiramine (Topamax) which is used in humans with partial and generalised seizures has also been used as an add on anticonvulsant in dogs with refractory epilepsy with no real improvement (anecdotal).

Diazepam can be used as an alternative to phenobarbitone in cats at a dose of 0.5-2mg/kg/day divided q8 hourly. Functional tolerance does not seem to develop to the anticonvulsant effects of diazepam in cats. Diazepam can cause idiosyncratic hepatotoxicity in cats. Diazepam should be discontinued if a cat becomes unduly sedated, lethargic or anorectic or vomits in the first week of treatment. A biochemical liver profile should be done prior to therapy and 3-5 days after treatment is started.

In dogs the short half life and rapid development of functional tolerance to the anticonvulsant effects of diazepam make it a poor maintenance anticonvulsant .

Clonazepam (Klonopin, Rivotrol) has been used as a treatment for acute and chronic seizures in humans. Tolerance to the anticonvulsant effects of clonazepam develop with repeated administration in dogs and it is not useful as a maintenance anticonvulsant drug.

Some animals with epilepsy will continue to have severe seizures and require intensive medical management despite daily medication. Increased frequency and severity of seizures is not necessarily an indication of underlying progressive disease. Approximately 20-30 % of epileptics will become refractory to all treatment. An increase the severity of seizures does not indicate an underlying progressive disease in most cases but brain damage can occur in refractory epileptics due to repeated seizures. Repetitive neuronal firing can result in cell death, brain hypoxia and /or hyperthermia due to inadequate ventilation and excessive muscle activity during prolonged seizures can all result in the development of cerebral oedema and cerebral ischaemia.

Desexing should be considered in all epileptic dogs. Females have a higher incidence of seizures during oestrus. Idiopathic epilepsy is likely to be genetic and therefore potentially heritable.

Emergency treatment of animal presented with refractory seizures (status epilepticus or repeated seizures-generalised or partial- without recovery between seizures)

- Provide O₂ if necessary and intubate if required
- Control seizures- place IV catheter and if animal is seizing administer diazepam 0.5mg/kg slowly IV to a maximum of 20mg/dog. If seizures do not stop administer propofol bolus to effect (1-5mg/kg) or thiopentone bolus to effect (sedation with seizure control not surgical plane of anaesthesia). IV diazepam may cause hyperexcitability in post ictal animals. Care in cats- diazepam can induce vasculitis in small vessels and should only be given IV via patent catheter.
- If unable to gain IV access can administer diazepam (dose above) per rectum (preferred) or IM. Cats can be anaesthetised with isoflurane or sevoflurane in a cat box. Self trauma associated with claws is a significant concern with seizing cats.

Midazolam can be used instead of diazepam IV or IM

- In an animal not known to be an epileptic- check blood glucose, calcium, urine ketones, electrolytes if possible and provide appropriate treatment if necessary. Blood can be drawn for a full CBC and biochemistry profile however values may be altered by prolonged seizures and not necessarily reflect the underlying cause.
- Check body temp and cool if necessary-wet towels, fan, cold water bath, cold water enema if necessary
- In animals without a previous seizure history (ie not a known epileptic) consider all possible causes of seizures (extracranial and intracranial) and formulate a diagnostic plan.
- For known epileptics record all medication given in the preceding 24 hours

If poisoning is suspected or possible (sudden onset severe seizures in a previously healthy dog) anaesthetise animal with propofol or thiopentone, intubate and maintain with isoflurane and O₂ to enable gastric lavage and/or enema and maintain anaesthesia until seizing stops (keep anaesthetised for 1 hour then try to recover-if seizing continues deepen plane of anaesthesia and repeat again in an hour).Take care to prevent aspiration. Alternatively, pentobarbitone IV can be given to effect (do **not give** calculated anaesthetic dose as bolus). Pentobarbitone currently difficult to access and does not prevent seizing on EEG. It does reduce muscle activity and apnea however that results in hypoxia and hyperthermia causing significant morbidity and mortality in status epilepticus.

If poisoning is unlikely and animal presented seizing -give Diazepam 0.5-1mg/kg IV (max 20mg per dog). This can be given per rectum if necessary. This dose can be repeated IV in 5 mins and per rectum in 20 minutes. No more than three doses of Diazepam should be given by any route in 24 hours. The depressive cardiac and respiratory effects increase with repeated doses and are much longer lasting than anticonvulsant effects.

IN ALL (known epileptics, suspect poisonings and seizures with as yet unknown aetiology) start **Phenobarbitone** at 2-10mg/kg (initially 2mg (cats)-4mg(dogs)/kg) IV,IM or PO q6-12hours. The dose given depends on what other drugs have been given and whether or not the dog is already receiving maintenance anticonvulsant medication. In dogs on phenobarbitone already a maximum cumulative dose (add amount given by all routes) is 20mg/kg q12 hours. In cats all doses (diazepam /phenobarb etc) should be halved.

Phenobarbitone will take 30 mins to be effective even if given IV and take>1hour for peak effect) but has a longer duration of action than benzodiazepines. Phenobarbitone and Diazepam act synergistically and can cause significant cardiovascular and respiratory depression. Animals need 24 hour care and monitoring as cerebral hypoxia and poor cerebral perfusion can result in further brain injury. Diazepam may also be associated with increased risk of aspiration.

If seizures are not controlled with Diazepam (max 2 doses) and phenobarbitone either;

- Bolus of propofol (0.5-5mg/kg) slowly to effect then constant rate infusion (0.05-0.5mg/kg/min. This is now standard treatment in humans with refractory seizures. Preferred option. Note recovery from propofol CRI may be prolonged in cats and prolonged use may cause Heinz body anaemia. If prolonged anaesthesia required in cats consider 2nd option

OR

- Anaesthetise with propofol or thiopentone (minimum dose required), intubate and maintain with isofurane (preferable) and O₂. Anaesthetise for at least 1 hour then lighten plane of anaesthesia. If still seizing reanaesthetise and repeat again in an hour. May be cheaper option than propofol infusion in larger dogs and 2nd preferred option.

OR

- Start constant rate infusion Diazepam 0.1-1mg /kg/hour added to 0.9% NaCl maintenance fluid requirement. Make up only 2 hours at a time as diazepam adheres to plastic of infusion line.

Start at lower end of dose recommendation and protect tubing from light. CRI of midazolam (0.1-0.5mg/kg/hr) may be used instead of diazepam. However continuous benzodiazepine administration in prolonged status epilepticus should be avoided as tolerance develops to Diazepam and may develop to Midazolam. Diazepam is probably a better anticonvulsant than Midazolam. If seizures continue beyond several hours switch to something else.

OR

- Anaesthetise with pentobarbitone to effect (not to surgical plane anaesthesia) and monitor carefully. Remember recovery from pentobarb anaesthesia often difficult to distinguish from seizures. Care needs to be taken not to overdose unnecessarily. Pentobarbitone is not an anticonvulsant.

In all of the above continue to give Phenobarbitone 2-10mg/kg/q 6-12 hourly IV, IM or SC.

Monitor respiration, blood pressure, temperature, hydration, and urine output. All of the above drugs will result in some degree of cardiovascular and respiratory depression, hypotension and reduced swallowing and lower oesophageal sphincter tone increasing the risk of aspiration pneumonia. IV fluids (monitor electrolytes after 48 hours), good nursing care, soft bedding and turning recumbent animals are imperative. Nutritional support may be necessary in animals that require treatment for longer than 72 hours.

Treatment with thiamine (thiamine dependent coenzymes necessary for glucose metabolism), a broad spectrum antibiotic and possibly a corticosteroid (single dose dexamethasone no more than 0.5mg/kg) should be given in animals with prolonged seizure activity requiring parenteral treatment for >24 hours).

Monitor neurologic status

Phenobarbitone should be continued PO (or parenterally if oral route not possible) until cause of seizures either resolved (eg poisoning) or established.

Neurologic abnormalities may be seen for days to weeks in animals after an episode of cluster seizures or status epilepticus regardless of the cause (including primary epilepsy) but neurologic status should improve. If neurologic abnormalities are persistent or

neurologic deterioration is seen in the absence of further seizures investigation for causes of progressive intracranial disease should be pursued.

For animals presented after a single seizure or having had a cluster of short seizures from which they recover quickly treat with Phenobarbitone 2-10mg /kg PO or IM and repeat q12 hours (dose depends on previous exposure to phenobarbitone). Phenobarbitone will take 30 mins to be effective even if given IV. If Diazepam is given -give per rectum if possible as effect is more prolonged and less hyperexcitability is associated with this route. **There is no point in giving an animal diazepam after a seizure unless dog has a history of cluster seizures with an interval between seizures of <1 hour. Diazepam should be given IV only if a seizure continues for more than 2 minutes.**

In animals that have a history of cluster seizures home management can be attempted. Diazepam 0.5-1mg/kg can be given per rectum (max 20mg per dog). This dose can be repeated in 20 mins and again in a further 20 mins. A maximum of 3 doses can be given in a 24 hour period. If seizures are still occurring with decreasing interval veterinary attention should be sought.

Some animals may also be managed with extra Phenobarbitone given orally. For a known epileptic up to 4 regular doses can be given in a 24 hour period (no more than 2x regular dose in 12 hours) for up to 48 hours in effort to reduce the number of seizures in a cluster.

NOTES:

Anticoagulant Therapy In Practice

Dr Graham Swinney

The recognition of disease in practice that warrants anticoagulant therapy is not straightforward. Thromboembolic disease or thrombosis does not have pathognomonic historical or physical examination findings, making a definitive diagnosis more challenging. Our ability to confirm thrombosis, or even a state where there is increased risk of thrombosis is also somewhat limited. When the decision has been made that anticoagulant therapy is necessary, the decision of what is the most appropriate therapy in a particular situation can also be difficult. This presentation will address the basics of haemostasis, discuss diseases that increase the risk of thrombosis or thromboembolism, some clinical manifestations of thrombosis, diagnostic strategies, and also therapeutic options when faced with the risk of, or the consequences of thrombosis.

CURRENT CONCEPTS OF COAGULATION IN DOGS AND CATS

Previous Models of Coagulation

The previous model of haemostasis was the Y model, which was developed in the 1960's, and has been modified and updated since that time. The theory was that there was a cascade of steps where enzymes cleaved proenzyme substrates, thereby generating the next enzyme in the cascade. The Y model consisted of intrinsic, extrinsic and common pathways. The intrinsic system was localised to the blood, and was initiated by the contact activation of factor XII in conjunction with other proteins. The extrinsic pathway included Tissue Factor (TF) and Factor VII, and was located 'outside' the blood. The common pathway began with the activation of Factor X to Factor Xa, which could be initiated by either the intrinsic or extrinsic pathways. Factor Xa with a cofactor, factor Va, then converted prothrombin (II) to thrombin (IIa), which subsequently cleaved fibrinogen (Ia) to fibrin (I).

When considering clinical evaluation of haemostasis the APTT (activated partial thromboplastin time) assesses the intrinsic and common pathways, and the PT (prothrombin time) evaluates the extrinsic and common pathways.

There are limitations with the system however when it is applied to haemostasis in vivo (i.e in the patient). The Y model suggests the extrinsic and intrinsic pathways operate independently, and are therefore redundant pathways, but both are necessary for normal haemostasis. However patients can have significant deficiencies of the initial components of the intrinsic pathway such as factor XII, high molecular weight kininogen (HMWK) and prekallikrein (PK), and have a significantly prolonged apt, but there will be no clinical bleeding tendency. However in Haemophilia A or B where there are deficiencies of factors VIII and IX respectively, and there can be serious haemorrhagic tendencies with an intact extrinsic pathway. A deficiency of factor VII can result in haemorrhage, despite an intact intrinsic pathway.

Cellular Localisation

It is important that for effective haemostasis that an obstruction is created at the site of injury, but coagulation needs to be avoided in sites where no injury is present. This is mainly achieved via the contribution of membrane surfaces to coagulation.

The speed of many of the enzymatic reactions in the coagulation process is altered by the presence of an appropriate membrane surface. Localisation/binding to a membrane surface in part speeds the reaction because it assists in properly aligning the participating proteins. Tissue factor is the only coagulation protein permanently attached to the membrane surface. Other coagulation proteins have gammacarboxyglutamic residues (G1a) that bind the protein to the membrane surface via a calcium dependant mechanism. The G1a proteins, which are factors II, VII, IX and X, require the Vitamin K cycle to properly develop the calcium and thereby membrane binding capabilities.

Normal cells have a lipid membrane bilayer that contains many constitutively expressed surface proteins. In a resting state there are neutral phospholipids on the external surface, and the negatively charged phospholipid phosphatidylserine (PS) and the neutral lipid phosphatidylethanolamine (PE) are localised to the inner surface of the membrane. When the cell is activated or injured, such as occurs with platelet activation, the PS and PE are actively shuffled to the outer surface of the membrane in response to increased concentrations of calcium in the cytosol. The expression of PS and PE on the cell surface has a profound impact on the procoagulant properties of the cell membrane surface. The presence of PS on the membrane increases the speed of some coagulation reactions – potentially thousands of times faster. The expression of these phospholipids on the cell surface turns it into a procoagulant

membrane. On resting cells the coagulation reaction occurs very slowly, so they do not effectively support the coagulation cascade, and the cells outside of the area of injury should be in a resting state. Therefore in an area away from the site of injury there will be insufficient generation of coagulation enzymes to produce enough fibrin to form a clot.

Microparticles are intact vesicles from cell membranes, and are primarily derived from endothelial cells, platelets and monocytes. In some disease states they may be derived from granulocytes, or erythrocytes (such as immune mediated haemolytic anaemia). They may be stimulated by cytokines such as TNF (tumour necrosis factor). Microparticles contain cell surface proteins similar to the parent cell, and can participate in coagulation reactions, especially if they express a procoagulant membrane. There will be elevated microparticle levels in disease states such as haematological diseases, sepsis, and cardiovascular disease including stroke or thromboembolic disease, or systemic disease such as diabetes mellitus or chronic renal failure.

Non-activated endothelial cells also express a number of other anticoagulant proteins on their surface. Endothelial cells produce heparan sulphated proteoglycans (HSPGs). The HSPGs are a binding site for antithrombin (AT), which can then inactivate thrombin in the vicinity of the HSPG. Resting endothelial cells also express thrombomodulin (TM) on their surface. Thrombin, once bound to TM, becomes an anticoagulant as the thrombin-TM complex rapidly activates protein C. Activated protein C (APC) and its cofactor protein S irreversibly cleave factors Va and VIIIa, meaning they can no longer participate in thrombin generation. The APC-protein S complex also inactivates plasminogen activator inhibitor 1, an important inhibitor of fibrinolysis. Thrombomodulin is expressed in much higher concentrations in capillary bed endothelium than the endothelium of major vessels. Tissue factor pathway inhibitor (TFPI) on endothelial cell surfaces acts as an upstream inhibitor of factor Xa and factor VIIa. TFPI binds irreversibly to factor Xa, and then forms a quaternary complex between TFPI, Xa, VIIa and TF, preventing their further participation in the generation of thrombin.

The Cell Based Model Of Haemostasis

This model recognises that coagulation occurs in vivo in overlapping phases, and requires the participation of two cell types – TF bearing cells and platelets. This model of haemostasis is classified into different stages including initiation, amplification and propagation.

Initiation

The sole initiator of coagulation in vivo is TF. The majority of TF expressing cells are outside the vasculature (keratinocytes, epithelial cells etc). Some circulating cells (monocytes, neoplastic cells) and microparticles may express TF on the membrane surface, but it is likely inactive.

Once an injury has occurred and flowing blood is exposed to a TF bearing cell, factor VII rapidly binds to the exposed TF. The TF-VIIa complex then activates a small amount of factors IX and X. The factor Xa generated binds to factor Va to form the prothrombinase complex, which subsequently cleaves prothrombin to form thrombin (IIa). Any factor Xa that dissociates from TF bearing cell surface is rapidly inactivated by TFPI or AT, but factor IXa can dissociate and move to the surface of nearby platelets or other cells, and it is not inactivated by TFPI, and is slowly inhibited by AT. The downstream coagulation factors are larger proteins and cannot escape the normal vasculature.

Coagulation only proceeds beyond the small amount of thrombin generated in the initiation phase when injury allows platelets and larger proteins to leave the vascular space and adhere to TF bearing cells in the extravascular space.

Amplification

Once a small amount of thrombin has been generated on the surface of a TF bearing cell, the thrombin is then available to activate platelets, and for activation of the cofactors V and VIII, and for generation of factor XIa. Binding of thrombin to platelet surface receptors activates the platelet – membrane phospholipid shuffling creates a procoagulant membrane surface and granule contents are released, adding ‘fuel to the fire’. The platelets granules contain proteins and materials for clotting reactions (vWF, HMWK, factor V), agonists to further activate platelets, and calcium.

Propagation

Once a few platelets are activated during amplification, granules are released that recruit additional platelets to the site of injury. Propagation occurs on the surface of these platelets. These platelets aggregate. Factor IXa generated by TF-VII interaction in initiation binds to factor VIIIa produced in amplification phase on platelet surfaces. Further factor IXa is generated by factor XIa generated during amplification. Factor Xa is then generated on the platelet

surface (the initial Xa from initiation is inhibited as it moves away from TF bearing cells) through cleavage of the tenase complex (factor IXa-factor VIIIa). The factor Xa generated rapidly binds to factor Va (generated by thrombin in amplification phase) and cleaves prothrombin to thrombin. There will be a burst of thrombin generation, with enough produced quickly to cleave fibrinogen, resulting in formation of a fibrin clot. Soluble fibrin is then crosslinked by factor XIIIa to form cross linked/insoluble fibrin. The thrombin must be generated on the platelet surface. This demonstrates why deficiencies of factors XI, IX and VIII cause clinical haemorrhage as they are required to generate factor X and subsequently thrombin on the platelet surface.

Coagulation is limited to the site of injury – even though some proteases diffuse away from the activated platelets and move downstream, there are no procoagulant cell membranes away from the site on injury. The activated protein C/protein S complex inactivates factor Va more efficiently on endothelial cells than on platelets, so little thrombin will be generated.

In summary;

1. Haemostasis is cell based – it occurs mainly on platelets and microparticles, and does not occur in the fluid phase.
2. Under physiologic conditions the coagulation cascade is initiated by TF (extrinsic pathway), and amplified by the intrinsic pathway (factor XI onwards). Factor XII contributes to clot formation in pathological arterial thrombosis.
3. Microparticles from leucocytes, platelets and endothelial cells increase the surface area on which coagulation can proceed and can bind to the surface of activated cells, localising coagulation factors sourced from different cells into a focal source. They may play a role in dissemination of coagulation in disease states.
4. Haemostatic pathways are all linked – platelets are necessary for secondary haemostasis, thrombin generated can activate platelets and inhibit fibrinolysis.

Activation of the Fibrinolytic Pathway

Fibrinolysis is initiated when plasminogen is activated to plasmin, which is achieved by tPA released from endothelial cells. Factor XIIa and bradykinin can also activate plasminogen and/or release tPA. Fibrinolysis is most efficient when tPA, plasminogen and c-terminal lysine residues of fibrin bind together as a complex.

Plasminogen binding amplifies plasmin generation and localises plasmin to the fibrin clot. Plasmin amplifies its own generation by exposing new lysine residues as it degrades fibrin. Plasmin cleaves fibrinogen, soluble fibrin and cross-linked fibrin. There are inhibitors of plasmin (antiplasmin) and tPA (plasminogen activator inhibitor I and II).

THROMBOSIS IN DOGS AND CATS

As discussed, haemostasis is a complicated process that involves the normal interaction and function of the vessel wall, platelets, von Willebrand factor, coagulation proteins, modifiers of coagulation, anticoagulants, and platelet inhibitors. In the normal situation coagulation will occur to prevent blood loss when vessels are damaged, but will be limited to the area of vessel wall injury. Once the vessel wall has been repaired, the clot will then be broken down to facilitate return of normal blood flow. If there is an imbalance in this system with reduced coagulation haemorrhage will occur, but if fibrinolysis is reduced, there is an increased risk of thrombosis.

When considering thrombosis pathophysiologically, there are three mechanisms that can contribute, and different processes that result in thrombosis have their effect via one or more of these mechanisms. There are;

1. Changes in the vascular endothelium
2. Alterations in blood flow
3. Hypercoagulability as a result of changes in platelets, coagulation proteins, or modifiers of coagulation.

The normal vascular endothelium as discussed earlier expresses anticoagulant properties. However when damaged, or it becomes dysfunctional it has the potential to have procoagulant properties. In humans atherosclerotic plaques promote thrombosis, and the same may be true in hypothyroid dogs. Vasculitis secondary to infectious or immune mediated disease can result in endothelial damage, as can a number of types of neoplasia, intravenous catheters, injections of irritating compounds. Elevated levels of homocysteine can result in vascular smooth muscle cell proliferation and inhibit endothelial cell growth. It is a risk factor for thrombosis in man, and possibly cats. Normal blood flow in vessels is laminar, with the faster flowing red cells in the centre of the vessel, and the white cells and platelets suspended closer to the vessel wall. Changes in vessel diameter result in a mixture of

turbulence and stasis of blood flow. Turbulence can result in vascular endothelial damage. Stasis can result in increased contact between platelets, coagulation factors and the vascular endothelium, promoting coagulation. A hypercoagulable state can result when there is an imbalance of the haemostatic system characterised by an increase in activity of platelets or coagulation factors, or a decrease activity of naturally occurring modifiers of coagulation such as antithrombin.

The clinical signs of thrombosis are related to end organ ischaemia. This may be local at the site of the thrombus, or if the thrombus (or part of it) dislodges and moves to a distal location it may be systemic (thromboembolism). Thromboemboli may be arterial or venous.

Arterial thromboemboli tend to have a more acute and severe clinical course. The classical location for arterial thromboemboli in dogs and cats especially is the aortic trifurcation, however any organ (for example renal or cerebral) or limb may be affected. Arterial thrombi are commonly termed white thrombi, as they form in areas of high blood flow, and consist primarily of platelets. Typically they form in the left atrium or ventricle, and dislodge distally. Clinical signs of acute arterial occlusion are described by the seven P's;

1. Pain
2. Pallor
3. Paraesthesia
4. Poikilothermia
5. Paralysis
6. Pulselessness
7. Prostration

In the case of venous thromboembolism, the thrombi form in a lower flow region, and are thus composed of fibrin and red cells, and are termed red thrombi. The clinical signs of these thrombi are typically less obvious, and may go undetected. Pulmonary thromboembolism would be an example of such a disease. Pulmonary thromboembolism (PTE) can be associated with a number of potential underlying diseases in veterinary medicine include dirofilariasis, immune mediated haemolytic anaemia, protein losing nephropathies and enteropathies, neoplasia, cardiac disease, trauma, sepsis, hyperadrenocorticism (spontaneous or iatrogenic), recent surgery and anaesthesia, disseminated intravascular coagulation (DIC), thrombocytosis, pancreatitis and snake bite. A number of these diseases result in a hypercoagulable

state because of loss of antithrombin (such as protein losing nephropathies and enteropathies for example). In the situation of immune mediated haemolytic anaemia, red cell fragments can act as a procoagulant membrane/surface. In patients with IMHA risk factors for PTE include intravenous catheters, icterus, hypoalbuminaemia, and elevated alkaline phosphatase levels. In hyperadrenocorticoid patients there may be increases in the levels of factors I, II, V, VII, IX, X and XII, along with a reduction in antithrombin concentrations. In DIC a disease process causing tissue damage results in activation of the coagulation system, resulting in thromboembolic disease, before there is consumption of coagulation factors that ultimately results in a haemorrhagic disease picture. In rare cases animals may be congenitally hypercoagulable because of deficiencies of proteins C or S or antithrombin.

The diagnosis of thromboembolic disease presents varying challenges. Arterial thromboembolism cases typically have pronounced clinical signs, such as those described above with a saddle thrombus. A clinical examination alone may result in a presumptive diagnosis of the thromboembolic disease. In other cases there could be a sudden onset of signs of ischaemia in other tissues, with resultant signs referable to that tissue (such as neurological signs with cerebral ischaemia, acute renal failure etc). Venous thromboembolism may have less typical clinical signs. In the case of pulmonary thromboembolism, a sudden onset of tachypnoea or dyspnoea may occur.

The evaluation of a blood count and biochemical profile helps to try and detect underlying disease. Checking for autoagglutination in the face of anaemia can help detect IMHA. A urinalysis and urine protein:creatinine ratio can help detect a protein losing nephropathy. Testing for dirofilariasis may be indicated based upon geographic location or travel history. A coagulation profile can help (but not definitively) rule in or out DIC. D dimers, which are a breakdown product of cross linked fibrin are considered a sensitive test in humans, but they are not readily available in veterinary medicine. Antithrombin III (AT III) levels can help suggest a hypercoagulable state, but again are not freely available.

The diagnostic confirmation of a hypercoagulable state can be challenging. Routine coagulation tests such as the prothrombin time (PT) and partial thromboplastin time are not typically helpful in the diagnosis of hypercoagulability. Antithrombin levels are not readily available. There is a technique called thromboelastography that is a whole blood based test that globally evaluates the coagulation system, but unfortunately it is also not readily available.

Thoracic radiographs would be part of the evaluation of a dyspnoeic patient. Changes are non specific however. There may be pulmonary changes that are interstitial, alveolar or lobar, which can be related to oedema, haemorrhage or infarction. Pulmonary arterial enlargement centrally, and abnormal vessel tapering may be noted. There may be cardiomegaly and mild pleural effusion. Up to 30% of dogs with PTE may have normal radiographs however.

Echocardiography may show thromboemboli, but only if they involve the heart or main pulmonary artery or the proximal branches. It is often most useful in cases of arterial thromboembolism to determine the underlying cause. Ventilation:perfusion scans can be helpful in diagnosis, but availability is strictly limited.

Pulmonary angiography is used regularly in humans to detect PTE. However the procedure is not without complications, and requires a general anaesthetic. Spiral CT scanning shows the most promise with respect to imaging studies.

Arterial blood gas analysis would be expected to be abnormal. Hypoxaemia is expected, as a consequence of the V:Q mismatch. Hypocapnia may be present reflecting hyperventilation.

Imaging studies can be used to identify thromboemboli in some cases, such as diagnostic ultrasonography, angiography, or magnetic resonance imaging.

THERAPY OF PATIENTS WITH THROMBOEMBOLISM

When considering therapy of patients at risk of, or with thromboembolic disease, options include anticoagulant therapy, antiplatelet therapy, and thrombolytic therapy. In any case of a patient with thromboembolic disease, supportive care will also be very important. Obviously attention will also need to be directed at therapy and ideally removal of the underlying disease process resulting in thrombosis, but this is not always possible.

Anticoagulant Therapy

Anticoagulants function via either direct or indirect interference with the coagulation cascade. Many are used for blood collection for transfusion therapy, such as citrate phosphate dextrose and acid citrate dextrose, functioning via removing calcium so it cannot be involved in the coagulation cascade, but they are not indicated

therapeutically. The drugs used for in vivo anticoagulation include heparin and the vitamin K antagonists such as coumadin. It is important to note that whilst these drugs help minimise the formation of further clots, they do not have any thrombolytic action.

Heparin

The discussion will be separated into material about the more traditional heparin (unfractionated), as opposed to newer low molecular weight heparin products. To understand the action of heparin, it is important to be familiar with the action of antithrombin. Antithrombin functions via the inactivation of serine proteases, most notably factor Xa, factor IXa and thrombin. This inhibition of serine proteases is significantly slowed in the absence of heparin, whereas binding of heparin results in a conformational change that increases its efficiency.

Unfractionated Heparin (UFH)

Heparin is a heterogenous mixture of negatively charged, polysulphated glycosaminoglycans. Other glycosaminoglycans include heparin sulphate, chondroitin sulphate and hyaluronic acid. Heparin and heparin sulphate are the most complex in this class of molecules, and are characterised by great biologic diversity. Heparin was named because of its initial discovery in the liver. It is stored in mast cells, basophils, and to a lesser extent in the vascular endothelium.

Commercially available heparin is derived from porcine intestinal mucosa or bovine lung. The molecular weight of heparin can vary from 5,000 to 30,000 daltons, but typical commercially available heparin has an average molecular weight varying from 12,000 to 16,000 daltons.

Heparin interacts with cell surface binding proteins and is internalised into cells by receptor mediated endocytosis. Heparin can bind to a wide range of proteins, some of which are not involved with coagulation. The anticoagulant activity occurs due a unique pentasaccharide sequence with a high binding affinity for antithrombin. Subsequent to this binding, the conformational change in antithrombin accelerates its activity some 1,000 to 4,000 fold, and possibly even 10,000 fold. Unfractionated heparin can bind to both antithrombin and thrombin to form a ternary complex that inactivates thrombin, but the anti Xa activity is only via binding of heparin to antithrombin.

Heparins also have an antiplatelet effect as a result of a high affinity for platelet factor IV. The effect is to reduce platelet aggregation, and it can negate the effect of platelet derived growth factor on vascular smooth muscle.

Heparin must be administered parenterally, either intravenously or subcutaneously. Intramuscular administration is not recommended as it can often induce local haematoma formation. It is rapidly absorbed when given subcutaneously. Heparin is metabolised by heparinase in the liver, and metabolites are eliminated in the urine. The elimination half life is likely molecular weight dependant, and is longer for smaller molecules. The half life is prolonged in the face of hepatic or renal dysfunction.

Unfractionated heparin has a number of limitations. The molecular weight can vary significantly, which can alter anticoagulant effects and pharmacokinetics. The potential influence on the half life is secondary to more rapid clearance of the larger molecules. The chain length also influences anticoagulant activity. Only 33% of the unfractionated heparin molecules contain the pentasaccharide sequence that is necessary to bind to antithrombin, and the distribution of the sequence within the molecule tends to be random. It was mentioned previously that heparin can bind to a number of proteins. In the situation of serious illness acute phase and inflammatory protein levels can be variable, and this can alter heparin bioavailability. The potential variable efficacy of heparin may result in either inadequate anticoagulation or over-anticoagulation. There is a narrow therapeutic index, and the drug also needs to be administered every six to eight hours.

Heparin can have potential side effects. It will interact with many drugs, so should never be mixed with other drugs. Haemorrhage can occur, and is the most common adverse effect. Other less common effects are heparin induced thrombocytopenia and osteoporosis. In human medicine there are two forms of the heparin induced thrombocytopenia. The milder form is manifest by a modest reduction in the platelet count within days in heparin naïve patients, or within hours if previously medicated. The mechanism is unknown. There have been studies of heparin use in normal dogs where there have been decreases in platelet counts. The more severe form is characterised by profound thrombocytopenia, because of antibodies directed at a platelet factor IV and heparin complex, but it has not been reported in dogs or cats.

Heparin can be used in the acute situation in the case of thrombosis, or can be used to try and prevent thrombosis occurring. The dose rates recommended for unfractionated heparin therapy are quite variable. Doses as low as 30-75 U/kg have been

suggested to prevent pulmonary thromboembolism. In more serious situations dosages ranging from 150-250 U/kg in dogs and 250-375 U/kg in cats, up to initial dosages of 500 U/kg. There is little clinical evidence to support the efficacy of any particular dosage regime. Studies in healthy dogs of effective dosages may not be applicable in unwell dogs. Some studies show little benefit from low dose heparin therapy. Unfractionated heparin therapy can be monitored via coagulation testing. A target PTT of 1.5-2.5 times the baseline, or an activated clotting time 1.2-1.4 times baseline in a sample collected two hours after dosing. There is not a linear relationship between heparin concentrations and prolongation of the PTT. Another way to assess heparin activity in plasma samples is the assessment of the anti-factor Xa activity. However it still has limitations in predicting the in vivo biological activity of heparin, because of variation in patient's antithrombin status, and it does not assess in vivo activity against thrombin. Thromboelastography may be a future technique for clinically monitoring heparin therapy.

Heparin therapy will be ineffective in the face of inadequate antithrombin concentrations. Therefore in cases where animals are hypercoagulable because of loss of antithrombin (PLE, PLN) heparin will be ineffective as a prophylactic anticoagulant. In such situations a plasma transfusion may be of benefit.

Gradual discontinuation of therapy has been recommended to avoid a rebound hypercoagulable state.

If patients are haemorrhaging as a consequence of heparin therapy, protamine sulphate can be used to complex heparin and reduce its effects. The dosage is reported as 1-1.5mg of protamine for each mg of heparin.

Low Molecular Weight Heparin (LMWH)

LMWHs like unfractionated heparin are glycosaminoglycans. However they are produced by enzymatic or controlled depolymerisation with resultant chains with a mean molecular weight of 5000. They possess the pentasaccharide region that binds to antithrombin. The relatively small size allows binding to antithrombin, but minimises concurrent binding to thrombin to produce ternary complexes, with a resultant anti-Xa activity to thrombin ratio of 4:1 as compared to 1:1 for unfractionated heparin. There are different LMWHs available, and they vary in pharmacokinetic and pharmacodynamic profiles. The LMWHs have much less binding to other proteins than UFHs, making the pharmacokinetics more predictable. There have longer half lives,

and there is a dose independent clearance, and are only administered subcutaneously. There appear to be less adverse effects when compared to UFHs. LMWH has been found to not alter platelet aggregability in dogs.

LMWHs are still under patent, so tend to be significantly more expensive than UFHs. Because of the mechanism of action being mainly anti-Xa activity, as PTT prolongation will typically not occur. Protamine sulphate will only partially reverse the effects of LMWHs as anti-Xa activity is incompletely inhibited.

There are no studies available in veterinary literature outlining the use of LMWH in naturally occurring disease. Experimental studies in dogs found the initially recommended dosages had limited efficacy, but more recent studies have shown more promising results. Experimental studies in cats suggest that they will require higher dosages and more frequent administration of the LMWHs.

Available low molecular weight heparins include dalteparin (Fragmin), and Enoxaparin (Lovenox). The dosage suggested in dogs for enoxaparin is 1 mg/kg q 12 hours, and the same has been previously suggested for cats. Dalteparin dosages are 100 u/kg q 12 hours, but 150 u/kg q 12 hours has also been suggested.

Oral Anticoagulants

Oral anticoagulants typically fall into the vitamin K antagonist class, and are sometimes used for chronic anticoagulant therapy. Warfarin would be the most commonly used drug in this group. This category of drugs interferes with the production of the vitamin K dependant clotting factors II, VII, IX and X. They exert their effect via the inhibition of an enzyme vitamin K epoxide reductase that reduces vitamin K so it can be used again (it is inactivated/oxidised during factor activation). These drugs also inhibit the hepatic synthesis of the anticoagulant proteins C and S. Serum concentrations of the anticoagulant proteins can fall more rapidly than the procoagulant factors, so patients may become hypercoagulable initially with therapy. It is typically recommended that heparin be administered concurrently with the warfarin for at least two to five days.

Warfarin is completely and rapidly absorbed orally. It has a half life of up to seven days, and is heavily protein bound. Metabolism of the vitamin K antagonists is hepatic to inactive metabolites, and then conjugation occurs. A number of factors can potentially increase the potency of warfarin, including hypoproteinaemia and hepatic disease. Antimicrobials that can interact with warfarin to

increase its activity include metronidazole, trimethoprim-sulphonamide combinations and some cephalosporins.

Initial recommended dosages for dogs are 0.1-0.2 mg/kg every 24 hours and 0.25-0.5 mg in cats. The effect of warfarin varies significantly between patients, so monitoring is essential. Initial recommendations were to maintain the PT at 1.5 times a baseline value. A standardised approach has been recommended based on an international reference preparation of standardised human brain thromboplastin. The International Normalised Ratio (INR) is calculated using the formula $\text{patient PT}/\text{control PT}^{\text{ISI}}$. The ISI is the International Sensitivity Index and is a value specific to the tissue thromboplastin being used in the particular PT assay. Studies documenting optimal doses of warfarin are lacking in veterinary medicine. The combination of warfarin and aspirin to reduce the risk of thromboembolism has been suggested, but there is a significantly increased risk of complications.

The main risk of warfarin therapy is haemorrhage, potentially fatal. The recommendation is for pets receiving the drug to be kept indoors to minimise the risk of trauma. If bleeding does occur the drug should be discontinued and vitamin K administered, or if acute haemorrhage fresh frozen plasma may be an option.

Antiplatelet Therapy

Platelet activity is controlled by substances generated both within and outside platelets. Adenophosphate, prostaglandins, thromboxanes, serotonin, cAMP and GMP are generated within platelets where they interact within the platelet or with receptors. Antiplatelet drugs inhibit platelet aggregation and adhesion, and can be used long term to try and help prevent rethrombosis.

Aspirin

Aspirin has long been used to inhibit platelet function. The drug irreversibly inhibits the specific enzyme (prostaglandin G and H synthetase) that catalyse the initial conversion of arachadonic acid to thromboxane A₂. There is a constitutive and inducible form of the enzymes, and the aspirin inhibits the constitutive form. Because platelets cannot synthesise proteins, they cannot regenerate the enzyme to form thromboxane A₂, so the platelet inhibition is irreversible.

The antiplatelet effects of aspirin can be separated from its other effects (such as anti-inflammatory, antipyretic) through dose modification. In dogs a dosage of 0.5 mg/kg every twelve hours is suggested. In smaller dogs a compounding pharmacy can formulate aspirin into appropriate dosages. Cats lack certain enzymes needed to metabolise aspirin (glucuronyl transferase), so the dosage recommended for cats is 25 mg/kg twice weekly. In cats with aortic thromboembolism there is a high recurrence rate even in the presence of aspirin therapy.

The clinical response to aspirin as an antithrombotic is variable, but is still typically recommended in dogs with clinical dirofilariasis to help minimise the risks of pulmonary thromboembolism. A recent study showed some potential benefit of the low dose aspirin dosage recommended in patients with immune mediated haemolytic anaemia with respect to minimising thromboembolic complications.

Ticlopidine

Ticlopidine is an antiplatelet drug that has been evaluated extensively in human patients at risk of thromboembolic disease. The drug impairs fibrinogen binding and inhibits platelet aggregation induced by ADP and collagen. The usage of ticlopidine has been limited in veterinary medicine. An experimental study in cats found a consistent antiplatelet effect with the drug, but there was dose dependant anorexia and vomiting.

Clopidogrel

Clopidogrel exerts its effects via irreversible inhibition of ADP receptors on the platelet membrane. There is hepatic metabolism with formation of one or more active metabolites. There has been some evidence that the drug can be useful in cats with aortic thromboembolism, starting at a dosage of 18.75 mg every 24 hours, in some cases administered concurrently with aspirin. The drug has also been used in dogs at risk of thromboembolic disease, with starting dosages of 0.5-1.0 mg/kg every 24 hours.

Thrombolytic Therapy

A number of drugs have been used intermittently as thrombolytics in veterinary medicine, including streptokinase, urokinase and tissue plasminogen activator (tPA). The success rates for these drugs are variable, and often low.

Streptokinase

Streptokinase is synthesised by streptococcal organisms. The drug binds plasminogen, and the complex converts other plasminogen molecules into plasmin. It will bind clot associated and free plasminogen. There is also an action to degrade factors V, VIII and prothrombin. The result is a significant coagulation defect.

Streptokinase has been used in some instances in cats with aortic thromboembolism. Initial dosages suggested in dogs and cats are 90,000 units intravenously over thirty minutes, followed by a maintenance infusion of 45,000 units over twelve hours. There is a risk of reperfusion injury, with potentially fatal hyperkalaemia and metabolic acidosis. The success rates reported are similar to success rates reported with conservative therapy.

Tissue Plasminogen Activator (tPA)

tPA, a serine protease is produced by recombinant DNA technology. tPA binds to fibrin forming a complex that activates clot associated plasminogen, resulting in rapid fibrinolysis. As with streptokinase there is a risk of reperfusion syndrome and haemorrhage. The half life of tPA is very short, so if haemorrhage occurs the infusion can be stopped and the drug will be cleared rapidly. A suggested dose rate in cats is 0.22-0.88 mg/kg/hour intravenously.

Surgery

Surgical embolectomy in cats with aortic thromboembolism carries a high risk. The cats typically have heart disease making them a poor anaesthetic risk. In addition there is a significant risk of reperfusion injury.

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NOTES:

Gastrointestinal Pharmacology

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ANTACIDS, ANTIEMETICS, EMETICS, PROKINETICS AND PROTECTANTS

Gastrointestinal disease is a common reason for presentation of dogs and cats to veterinary clinics. Obviously there is a myriad of diseases that can affect the gastrointestinal tract, either primarily or secondarily. This presentation cannot obviously cover all aspects of potential therapies for gastrointestinal disease. It will cover aspects of antacid, protectant, antiemetic, emetic and prokinetic therapy, and assist in making sense of the many choices available in these situations.

EMETIC AND ANTIEMETIC THERAPY

The Vomiting Reflex

Before discussing antiemetic therapy it is very important to understand the vomiting reflex. This can help then determine the appropriate therapy for an individual patient. Vomiting may be secondary to gastrointestinal or extra-gastrointestinal disease, such as metabolic diseases, toxins, central nervous system disease, or other systemic illnesses.

At its most basic level, vomiting is a protective mechanism to remove toxic or noxious ingested substances from the gastrointestinal tract. In some animals it is used for the feeding of ingested food to offspring.

The act of vomiting has three phases – nausea, retching and vomiting.

1. Nausea – This phase precedes vomiting, and is harder to define in animals than man. Clinical signs of this phase may include obtundation, hiding, shivering, yawning and lip licking. Increased salivation and swallowing occur, which serves to line the oesophagus with bicarbonate rich saliva to help neutralise the gastric acid that will soon enter the

oesophagus. Also occurring in this phase is reduction in oesophageal, lower oesophageal sphincter and gastric motility (likely mediated by dopaminergic receptors), and then increased retrograde motility in the proximal small intestine.

2. Retching – In this phase there are forceful contractions of the diaphragm and abdominal musculature. This produces a negative intrathoracic pressure, which aids in the movement of gastric contents into the oesophagus.
3. Vomiting – The final phase is achieved by contraction of the diaphragm and abdominal musculature. This increases the intrathoracic pressure that was low in the retching phase to a positive pressure. This results in the forceful expulsion of the material in the oesophagus via the mouth. During this phase the glottis and nasopharynx are occluded to avoid contamination.

Vomiting is a complex reflex that is neurologically mediated, and is initiated by the vomiting or emetic centre that is located in the lateral reticular formation of the medulla oblongata in the brain stem. The vomiting centre itself is afforded protection by the blood brain barrier. There are a number of different pathways responsible for causing vomiting, but all signals are co-ordinated by the vomiting centre. Some stimulation is humoral via blood borne substances, but much of the stimulation is through stimulation of neural receptors and other pathways to the vomiting centre. In the medulla adjacent the vomiting centre are regions for control of respiration and salivation, which aids in the co-ordination of all these activities.

Impulses to the vomiting centre may arise from higher centres in the brain, including the cerebral cortex or limbic system. Stimuli can be the result of inflammation, hydrocephalus, or other space occupying lesions. Head injuries and increased intracranial pressure initiate vomiting via the limbic system. In contrast psychogenic vomiting as a result of fear, stress, pain, or visual or olfactory stimuli act via the cerebral cortex. Acetylcholine is the primary neurotransmitter that mediates the vomiting induced by these higher centres, although histamine acting on H1 receptors may act as a secondary neurotransmitter.

The vomiting centre can be stimulated indirectly by humoral activation of the chemoreceptor trigger zone (CRTZ) in the area postrema in the lateral walls of the third ventricle. The blood brain barrier is incomplete in this area, rendering it more susceptible to circulating drugs or toxins than the vomiting centre itself. The

neurones in the CRTZ have increased sensitivity to blood-borne and cerebrospinal fluid (CSF) borne chemicals as there are free nerve endings in direct contact with the CSF. There is a long list of substances that can stimulate the CRTZ include metabolic toxins (uraemic, hepatic, electrolyte, osmolar, ketones, acid base) and bacterial toxins. There are a number of drugs that can stimulate the CRTZ including cardiac glycosides, apomorphine, opioids, chemotherapy agents, xylazine and a number of antimicrobial agents. Some ingested toxins such as ethylene glycol can also induce vomiting.

Stimulation of the CRTZ is initiated by dopaminergic receptors (D2) that respond to agonists such as dopamine or apomorphine. Serotonin (5-HT₃) is also an important mediator to induce emesis via the CRTZ. Histamine (H₁) is a secondary neurotransmitter in the CRTZ. There are a number of subreceptor types for each neurotransmitter – with at least five for dopamine, nine serotonin and five histamine – and the drugs active in the CRTZ potentially have affinity for certain types of subreceptors. Alpha 2 receptors in the area postrema can also induce emesis. The dopaminergic receptors are poorly developed in the cat, which explains the generally poor response to apomorphine as an antiemetic in this species.

Impulses originating in the peripheral vestibular system are transmitted via the vestibular nerve to the vestibular nuclei in the brain stem, and are then transmitted to the CRTZ and then to the vomiting centre. This pathway is mediated by histaminergic receptors, and is responsible for the vomiting associated with motion sickness, labyrinthitis or cerebellar lesions.

Neural stimulation of the vomiting centre can arise through afferent pathways including vagal, sympathetic, vestibular, glossopharyngeal and cerebrocortical. Stimulation of peripheral receptors distributed around the body can stimulate the aforementioned neural pathways. Locations of receptors include the heart, stomach, duodenum, small intestine, liver, gall bladder, peritoneum, kidneys, ureters, bladder and uterus. The receptors in the abdominal viscera are considered most important, with the highest concentration of receptors in the duodenum, which is a common source of nausea. The majority of the receptors in the abdominal organs have their effect on vomiting via vagal afferents, whereas those in the kidneys, uterus and bladder transmit via sympathetic afferents. The receptors in the pharynx and fauces transmit via the glossopharyngeal nerve.

Emetic Therapy

Emetics may be indicated to empty the upper gastrointestinal tract. This may be indicated in the case of potential ingestion of non corrosive toxins, or to empty the stomach prior to a general anaesthetic.

Emesis can be induced peripherally by distension of the pharynx, oesophagus, stomach or duodenum with water, hydrogen peroxide (0.25-0.5 ml/kg) or saline. Other compounds induce emesis via irritation of the gastrointestinal epithelium, such as oral administration of a strong sodium chloride solution, pharyngeal placement of salt, or oral administration of 3% hydrogen peroxide. In all cases there is some potential risk of aspiration, and in some cases of aspiration of foam from hydrogen peroxide it has been fatal. Care must be taken using salt, as if large doses are given and vomiting does not occur, hypernatraemia may result.

Ipecac syrup contains the alkaloid emetine, which can cause lacrimation, salivation and increased bronchial secretions. Emesis can occur from both peripheral and central stimulation. There should only be a single repeat of a dosage if emesis does not occur to avoid toxicity. The suggested dosage is 2-6 ml by mouth.

Centrally acting emetics typically stimulate the CRTZ, and some opiates fall into this category. One of the more commonly used drugs is apomorphine hydrochloride, which is a synthetic derivative of morphine. Its emetic actions are greater than its morphine like actions. The emetic action is via stimulation of dopaminergic receptors on the chemoreceptor trigger zone. The drug can be administered by many different routes, including intravenously, subcutaneously, orally or conjunctivally. Oral dosages are higher because of the lower bioavailability. There was a recent study comparing 5,000 dogs treated with oral apomorphine and 32 with the drug intravenously. The success rate (vomiting induced within fifteen minutes) for the conjunctival group was 83.5% and the intravenous group 90.6%. Ocular irritation occurred in the conjunctival group, but adverse effects were more common in the intravenous group. Adverse effects can include central nervous system and respiratory depression. Apomorphine is not recommended if there is significant pre-existing respiratory depression. Apomorphine, whilst stimulating the CRTZ can also directly depress the emetic centre, so if the initial dosage is ineffective, repeated dosing is unlikely to be of benefit. As discussed earlier, the poor development of the dopaminergic receptors in cats makes the apomorphine an unreliable antiemetic in that species.

Xylazine acts as an alpha 2 agonist. When administered at subsedative dosages in cats (0.05 mg/kg) it can be an effective emetic. It is less reliable with respect to this action in dogs.

Antiemetic Therapy

Antiemetics can have action centrally or peripherally. In both situations their actions depend on blockade of neurotransmission. Centrally acting antiemetics have their actions at the higher centres including the vomiting centre (such as muscarinic anticholinergics), the CRTZ (such as antidopaminergics which primarily block dopaminergic receptors, or antihistamines), and the vestibular apparatus (antihistamines that block H1 receptors).

Non selective cholinergic receptor antagonists such as atropine or scopolamine are typically not recommended as they can cause ileus, delayed gastric emptying and a dry mouth. There is a selective M1 antagonist pirenzepine, but it is not available.

Drugs Acting at the Chemoreceptor Trigger Zone

Metoclopramide

Metoclopramide is a lipid soluble derivative of para-amino-benzoic acid, and is structurally related to procainamide. It blocks vomiting induced by the CRTZ. It was initially felt that its anti-dopaminergic action (D2) was the main antiemetic mechanism, but it is now considered that antagonism of the 5HT3 serotonergic receptors is the primary mechanism of action. It also has cholinergic effects on smooth muscle. It effectively antagonises apomorphine induced emesis. Metoclopramide also has peripheral effects. It physically antagonises vomiting by increasing the tone of the lower oesophageal sphincter, a gastrokinetic action, relaxing the pyloric sphincter, and the promotion of peristalsis in the duodenum and jejunum, accelerating gastric emptying and upper intestinal transit.

Metoclopramide is well absorbed orally, but as there is significant first pass metabolism the bioavailability is 50-70%. The plasma half life is approximately 90 minutes, so the duration of action is relatively short. Excretion is renal and hepatic. The drug is contraindicated in cases of gastrointestinal obstruction or perforation, and also likely in patients with seizures. There are dose dependant central nervous system side effects, including nervousness, restlessness, depression and disorientation. Extrapyramidal

antidopaminergic effects can include tremors. Its effects can be antagonised by atropine and opioid analgesics.

Metoclopramide can be given orally or parenterally. For parenteral use intermittent dosing is possible, but a continuous rate intravenous infusion is often the most effective. Metoclopramide is less effective in cats.

Phenothiazines

Examples of drugs used in this class are prochlorperazine and chlorpromazine. These drugs antagonise a number of receptors, including α_1 and α_2 , H1 and H2 histaminergic and D2 dopaminergic receptors in the CRTZ and at higher doses possibly in the vomiting centre.

Prochlorperazine has weak anticholinergic effects, strong extrapyramidal effects, and moderate sedative effects. It has strong antiemetic effects. It should be avoided if patients are hypotensive, or concurrent fluid therapy administered. The dosage should be reduced in the face of cardiac or hepatic disease. They are often indicated when metoclopramide has failed.

Serotonin Antagonists

The serotonin antagonists have their primary action at the CRTZ, and have been suggested as useful for their antiemetic effects, especially for chemotherapy induced vomiting. Whilst cyproheptadine has other uses in dogs and cats (it also has anticholinergic and antihistaminergic actions), and is sometimes used to control vomiting in humans, it is rarely used for this purpose in small animals.

Ondansetron is a potent antiemetic used in human patients undergoing chemotherapy. The release of serotonin from mucosal enterochromaffin cells in the small intestine may play a role in chemotherapy induced vomiting. It is unclear if its antiemetic actions are through action on serotonergic receptors on vagal nerve terminals peripherally or centrally in the CRTZ. It has typically been reserved in dogs for patients with intractable vomiting non responsive to other antiemetics. Veterinary studies on pharmacokinetics are lacking, but in humans there is mainly hepatic metabolism. Care should be taken in patients with hepatic

insufficiency, and dogs with the MDR-1 defect may have increased sensitivity as it is potentially a substrate of p-glycoprotein. Potential side effects include constipation, extrapyramidal symptoms, cardiac arrhythmias or hypotension. The use of ondansetron is not recommended in cats. Both oral and parenteral forms of the drug are available.

Dolasetron is also a serotonergic receptor antagonist, similar to ondansetron. The main advantage over ondansetron is that it can be administered once daily. The drug is rapidly reduced via carbonyl reductase to hydrodolasetron, which is primarily responsible for the drug's pharmacological effect. The drug is rapidly absorbed orally. In humans whilst there is some hepatic metabolism, much of the drug is excreted unchanged in the urine. The drug is contraindicated in patients with second or third degree atrioventricular blocks. Atenolol or cimetidine may reduce the clearance of dolasetron increasing its blood levels.

Drugs Acting at the Vestibular Apparatus

Antihistamines

As discussed previously, motion sickness is mediated by the vestibular apparatus. Antihistamines such as meclizine or diphenhydramine can help control motion sickness in some animals. Meclizine is also sometimes used for the nausea associated with vestibular disease.

New Antiemetics

Maropitant

Maropitant is a neurokinin-1(NK-1) inhibitor that has been developed as an antiemetic. Substance P is a potent agonist of the NK-1 receptor. Maropitant is a synthetic, non peptide NK-1 receptor antagonist. It distributes into the brain and inhibits the effect of substance P within the central emetic circuitry. Because of this central action, it is claimed to have a broad spectrum anti emetic action. It can be administered by subcutaneous injection or orally. First pass metabolism contributes to a significantly lower oral bioavailability, necessitating higher oral dosages of the drug. Once daily dosing appears to be sufficient. Oral absorption is not affected by food.

The drug has been recommended to help prevent motion sickness in dogs. Studies suggest that it is more effective than metoclopramide in the treatment of vomiting caused by many different aetiologies. It has been shown to be effective in the treatment and prevention of cisplatin induced emesis in dogs.

Miscellaneous Antiemetics

Glucocorticoids, particularly dexamethasone, can have some antiemetic effect, by an unknown mechanism, especially in the situation of chemotherapy. They can act in a synergistic fashion with other antiemetics. However because of the potential side effects, their routine use in this situation is not recommended.

In contrast to the potential emetic action of some opioids, butorphanol can have a potential antiemetic action during the administration of cisplatin.

Peripherally Acting Antiemetics

In some cases gastric protectants such as sucralfate can be used to bind toxins and can protect the gastrointestinal mucosa in cases of gastritis or ulceration, and the subsequent reduction in irritation may reduce vomiting. The use of antacids may achieve a similar end if there is ulceration or erosion present. The use of mucosal cytoprotectants such as prostaglandin analogues when non steroidal anti-inflammatory drugs are being used may also be of benefit. Prokinetic drugs also have potential benefits to reduce vomiting. All these drugs will be discussed in the notes.

GASTROINTESTINAL ULCERATION AND ANTACID THERAPY

There is normally a balance between acid secretion and the defence mechanisms in the gastrointestinal tract to maintain a normal mucosal barrier. If there is some imbalance in this system gastrointestinal ulceration may be the result. The gastric mucosal barrier consists of tightly opposed epithelial cells that are coated with a layer of bicarbonate rich mucus. A plentiful mucosal blood supply is also vital to deliver oxygen, bicarbonate and other nutrients. The local production of prostaglandins (PGE₂) has a central role in modulating blood flow, bicarbonate secretion and epithelial cell renewal. If there is damage to the mucosa epithelial cells rapidly migrate over superficial mucosal defects under the influence of factors such as epidermal growth factor.

Factors that can result in damage to the gastric mucosal barrier include impairment of the gastric mucosal barrier through direct damage, interference with the gastroprotective prostaglandins, mucous or bicarbonate, reduced blood flow, or hypersecretion of gastric acid.

Gastric acid secretion occurs in four phases. The first three phases are referred to as cephalic, gastric and intestinal, and are stimulated by food, and mediated by gastrin. During these phases the acid secretion is persistent, and the gastric pH will gradually decrease as the nutrients pass through the gastrointestinal tract. Gastrin secretion reduces once the gastric pH falls to 3.5, and is completely inhibited at a pH of 1.5. The fourth phase of secretion is basal and occurs without external stimuli.

Gastric acid secretion involves the generation and secretion of hydrogen ions by the parietal cells of the gastric mucosa. The hydrogen ion pump is unique as it is a hydrogen-potassium ATPase system. There are three pathways that can stimulate acid secretion. The neurocrine system involves acetylcholine interacting with muscarinic receptors located on parietal cells. The endocrine pathway delivers gastrin which interacts with gastrin receptors. The paracrine pathway delivers histamine which interacts with H₂ receptors on the parietal cell. In contrast prostaglandins of the E series modulate the above effects, inhibiting gastric acid secretion by blocking cAMP production.

There are a number of disease processes that can cause gastric ulceration. These may be primary gastrointestinal in nature, such as inflammatory disease or neoplasia. There are many secondary causes such as metabolic diseases (hepatic disease, kidney disease), endocrine diseases (hypoadrenocorticism), drugs (non steroidal, glucocorticoids), neoplastic disease (gastrinoma, mast cell neoplasia), shock, sepsis, disseminated intravascular coagulopathy, exercise induced in sled dogs, spinal cord disease, or potentially stress. Some of the most common causes encountered in practice are ulcers induced by non steroidal anti-inflammatory drugs, and those induced by glucocorticoids, either alone, or in cases with spinal disease where they are administered. In the case of older NSAIDs, there is direct mucosal damage, along with reduced prostaglandin synthesis. To lessen the effect on the helpful prostaglandins, drugs have been developed to preferentially target the inducible cyclo-oxygenase (COX-2). Whilst they have less ulcerogenic potential some risk still remains.

Gastric Antisecretory Drugs

Drugs that have activity to modulate gastric acid secretion include H₂ receptor antagonists, proton pump inhibitors, prostaglandin E₂ analogues, and anticholinergics. Even though acetylcholine stimulation of muscarinic receptors stimulates gastric acid production, anticholinergics have been proven ineffective for control of gastrointestinal ulceration in animals. Care must be taken with longer term use of any drug that can alter the gastric pH as achlorhydria can result in an increased risk of bacterial overgrowth, and reduced absorption of some nutrients, including vitamin B₁₂.

H₂ Receptor Antagonists

The H₂ receptor antagonists cause reversible, competitive inhibition of hydrogen ion secretion in the stomach, and also pepsin secretion. Drugs in this category include cimetidine, ranitidine, famotidine and nizatidine. Cimetidine has the longest history of use of these drugs. It has the lowest potency, with ranitidine five to twelve times as potent. Famotidine is about nine times as potent as ranitidine in suppressing gastric acid production, and also has the longest duration of action. Ranitidine and nizatidine also have some prokinetic actions.

Cimetidine is rapidly absorbed from the gastrointestinal tract, but this can be delayed to some degree by food. There is hepatic metabolism, and oral bioavailability is about 70%. Excretion is urinary, both in the unchanged and conjugated forms. The plasma half life is approximately one hour, but hepatic and renal disease may prolong this. Cimetidine has a number of drug interactions. Like any drug that increases gastric pH, the absorption of drugs that are weak acids will be reduced. Cimetidine may bind to some drugs directly, affecting their absorption. Most importantly cimetidine is a potent inhibitor of the hepatic microsomal enzyme system (cytochrome p-450), which can affect the hepatic metabolism of other drugs, with resultant toxic effects of these drugs. Occasionally this enzyme secretion is exploited therapeutically, such as in the case of paracetamol toxicity in cats. Cimetidine may also reduce hepatic blood flow by up to 20%, which can reduce clearance of 'flow limited' drugs such as propranolol and lignocaine.

Ranitidine has a lower oral bioavailability at approximately 50%, and this is not affected by the presence of food. The elimination half life is two and a half hours. There is minimal protein binding. Hepatic metabolism is responsible for the elimination of 30% of

intravenous doses and 73% of oral doses. There is minimal effect on hepatic blood flow or metabolism of other drugs.

Famotidine has poor oral absorption, and is 37% bioavailable after oral dosing. It is predominantly excreted unchanged in the urine. As with ranitidine, there is limited to no effect on hepatic blood flow or metabolism of other drugs.

In humans treated with H₂ receptor antagonists there is a described phenomenon of relapse of gastroduodenal ulceration after therapy with H₂ receptor antagonists is discontinued. This is most likely due to a rebound gastric hyperacidity. During therapy with the H₂ receptor antagonist, gastric pH rises, with a resultant increase in gastrin concentrations. This stimulates gastric acid hypersecretion that becomes apparent once the drugs are discontinued. This is most common with cimetidine, and least common with famotidine.

There are many clinical indications for therapy with these drugs. They include erosive gastritis with stress, gastrinoma, mast cell neoplasia, uraemic gastritis, or cases of upper gastrointestinal bleeding where there is not erosion of major blood vessels. They may also be helpful in situations such as gastro-oesophageal reflux, oesophagitis and duodenal-gastric reflux. In the situation of NSAID induced ulcers, they may be less effective than the prostaglandin analogues. Ranitidine is likely less effective than famotidine at reducing gastric pH.

Proton Pump Inhibitors

The proton pump inhibitors are potent and irreversible antagonists of the hydrogen, potassium ATPase pump, which is the final step in gastric acid secretion, no matter which secretagogue is involved. Omeprazole, a substituted benzimidazole, is the most commonly used drug in this class in veterinary medicine. It is a weak base and is unstable in an acidic environment, so the human form of the drug is formulated as encapsulated enteric coated granules. The oral bioavailability increases with increasing pH, so plasma drug concentrations tend to increase over a few days. Omeprazole is metabolised hepatically, and the metabolites are excreted in the urine. The drug is highly protein bound. The drug concentrates in the gastric parietal cells, and there may be a lag phase of three to five days before its full effects. The serum half life in dogs is as little as one hour, but the clinical effects last twenty four to seventy two hours. In the parietal cells there is potent and permanent inhibition of potassium adenosine triphosphate. New enzyme must be generated to result in hydrogen ion secretion.

Adverse effects are few as its effect is narrow. Diarrhoea and transient changes in the liver enzymes have been reported. There is some inhibition of the cytochrome p-450 enzyme system, and it may slow the elimination of diazepam or warfarin, but the effects are significantly less than those of cimetidine. Hypertrophy of gastric mucosa has been reported, and the gastric acid secretory capacity may increase (secondary to hypergastrinaemia).

Omeprazole is indicated for serious gastric ulceration, or in cases where H₂ receptor antagonist therapy has been unsuccessful. It has been shown to be the drug of choice for treating patients with gastrinoma (Zollinger-Ellison syndrome). In some patients affected by gastrinoma, omeprazole has been combined with a long acting somatostatin analogue Octreotide. As with H₂ receptor antagonists, omeprazole is not effective in preventing glucocorticoid induced gastric ulceration, or in those with spinal disease treated with glucocorticoids.

Mucosal Protectants

Sucralfate

Sucralfate is polyaluminium sucrose sulphate, which binds to and protects ulcerated sites from gastric acid, bile and pepsin. In an acidic environment the sucrose is freed from the aluminium hydroxide, and then cross polymerises and binds to exposed anions of the gastrointestinal epithelial membrane. Binding occurs in the base of the ulcer crater, and occurs to a greater degree in the duodenum than the stomach. The sucralfate also binds to and inactivates bile acids and pepsin. The polymerised sucrose also minimises exudation of protein and electrolytes into the gastric lumen. There may be some neutralisation of gastric acid by the aluminium hydroxide, but the dose is typically not high enough to achieve this to a great degree. Sucralfate may also stimulate the formation of local mediators to protect the gastric mucosa such as enhancing prostaglandin synthesis and free radical scavengers. It may increase local blood flow via the prostaglandin effect or the induction of local nitric oxide. Sucralfate may also bind epithelial growth factor increasing its concentration in mucosal lesions.

Sucralfate is minimally absorbed, and has minimal side effects. It requires an acidic environment for activation. It may bind and reduce the absorption of other drugs administered concurrently orally. Therefore administration should be separated from other oral drugs by two hours. It is useful in many cases with gastrointestinal ulceration, or may be used in illnesses where there is increased risk of ulceration. It can also be used in cases with reflux oesophagitis.

Prostaglandin Analogues

The prostaglandins of the E series may have some effect to reduce gastric acid secretion. After interaction with the basolateral membrane receptor, there is a reduction in intracellular concentrations of cAMP, which reduces protein kinase activity, and thereby hydrogen ion production reduces. This is not the primary effect however, which is a cytoprotectant action.

Misoprostol is a methyl ester analogue of prostaglandin E1. It has primarily a local action, as the majority of any absorbed drug is rapidly metabolised by the liver. Locally it increases mucous and bicarbonate secretion, enhances mucosal blood flow, and increases epithelialisation of the mucosa. Basal, nocturnal and food induced gastric acid secretion is reduced by misoprostol, but as mentioned before it is not as effective to this end as H₂ receptor antagonists or proton pump inhibitors. Unabsorbed drug may reach the intestines where it can increase secretion and smooth muscle contraction, with resultant diarrhoea. The primary indication is preventative or therapeutic with ulcers associated with NSAID therapy. Misoprostol is ineffective at preventing ulcers induced by glucocorticoids. It should not be used in pregnant animals, and gloves should be worn when handling the drug.

MODULATORS OF GASTRIC MOTILITY

Normal gastric motility is the result of an organised interaction between smooth muscle and neural and hormonal stimuli. Regulation and integration of gastrointestinal motility is mediated by the interaction of chemicals on the receptors of target cells. This includes neurocrines (chemicals delivered by nerves), hormones or endocrine stimulation (chemicals delivered via the blood stream), and paracrines (chemicals delivered by diffusion through interstitial fluid. In addition there is an extrinsic system, which consists of the vagal and sympathetic nerves, and an enteric or intrinsic system of nerves and ganglia situated between the longitudinal and smooth muscle layers that help control activity of the GI tract.

There are a number of different receptors in the gut. Generally cholinergic neurones stimulate gastric motility and adrenergic receptors inhibit gastric motility. Stimulation of histamine H₁ receptors induces smooth muscle contraction, whereas H₂ receptors stimulate relaxation. The role of dopamine and serotonin in GI motility is complex and not fully understood. Antagonists of D₂ and 5HT₄ receptors generally stimulate gastric motility.

The rate of gastric emptying is determined by the difference in pressure between the stomach and duodenum, and the resistance to flow across the pylorus. Liquids exit the stomach more quickly than solids, and the rate of emptying of liquids increases with volume. The rate of expulsion of solids varies with caloric density. Carbohydrates, amino acids and especially fats slow gastric emptying, partially mediated via cholecystokinin release. Large, indigestible solids are expelled from the stomach in the fasted phase by the migrating motility complex under the influence of motilin.

Three types of gastric motility disorders are recognised, including accelerated gastric emptying, retrograde transit (enterogastric or gastro-oesophageal reflux) and delayed gastric emptying. Mechanical causes of obstruction are easier to diagnose and potentially correct with surgery. If there is a mechanical obstruction prokinetic agents are contra-indicated. Functional obstruction is typically diagnosed after mechanical obstruction has been ruled out. Potential causes of a functional obstruction include primary gastrointestinal disorders such as recovery from gastric dilatation/volvulus, infectious disease (such as parvovirus), inflammatory disease, ulcers, or post surgical. Altered gastric motility has been reported secondary to electrolyte abnormalities (hypokalaemia), drugs (anticholinergics, opioids), stress and abdominal inflammation (pancreatitis, peritonitis). In many cases the cause goes undetermined.

Therapy should be directed at the primary cause if possible. Dietary modification can be used in cases of delayed gastric emptying. The dietary therapy is based on principles mentioned previously. Liquids empty from the stomach more quickly than solids. Carbohydrates empty faster than proteins which are faster than fats. A semi liquid, low fat, low protein diet can be used, with rice or pasta added.

Prokinetic drugs enhance the transit of intraluminal contents. They function by promotion of an agonist, such as muscarinic drugs, or inhibition of an inhibitory neurotransmitter such as dopamine. They should only be used if there is no obstruction. Common choices include metoclopramide, cisapride, erythromycin or rantidine. The choice of drug may vary depending whether concurrent antiemetic action or antacid action is required.

Cholinergics

Cholinergics can have a prokinetic effect, but their variable action and regular side effects limits their usage. Side effects can include abdominal cramps, diarrhoea, salivation and bradycardia.

Metoclopramide

Metoclopramide has been discussed previously with respect to its antiemetic properties and its pharmacokinetics. Its prokinetic activities are mediated via a number of mechanisms, including being a D2 dopaminergic antagonist, an alpha 2 adrenergic antagonist, a beta 2 adrenergic antagonist, a 5-HT4 antagonist and a 5-HT3 antagonist. It is often the initial choice as a prokinetic. Its activity is limited however to the stomach and upper small intestine. Whilst it can help minimise gastro-oesophageal reflux in conscious patients, it is less effective in this role in anaesthetised animals, and requires much higher dosages.

Domperidone

Domperidone is a dopamine antagonist with prokinetic properties similar to those of metoclopramide (D2 dopaminergic antagonist, and alpha 2 and beta 2 adrenergic antagonist). There is no anticholinergic activity. It accelerates small intestinal transit, but has little activity in the large intestine.

Cisapride

Cisapride is a broader spectrum prokinetic agent than metoclopramide, with dose dependant increase in activity in the stomach, jejunum, ileum and colon. It has actions via indirect stimulation of cholinergic nerves. It is a 5-HT4 agonist, possibly via an action at the myenteric plexus. It also has actions as a 5-HT1 and 5-HT3 antagonist, and a 5-HT2 agonist. Prokinetic effects have been documented in the stomach, small intestine and colon. It was suggested initially as a potential drug for use in idiopathic canine megaesophagus. However as the majority of the canine oesophagus is skeletal muscle, it is likely of less benefit, and experimentally it delayed motility with cisapride in normal dogs. Theoretically it may be more beneficial in cats. In cats cisapride has been shown to stimulate motility in the colon in cats with idiopathic megacolon.

Cisapride is well absorbed after oral administration. It undergoes first pass metabolism, and oral bioavailability is 30% in cats, with a half life of five hours. Elimination will be slowed in the presence of liver disease. The availability of cisapride is limited, because of drug interactions in humans resulting in sudden cardiac death. The risk was higher when the drug was combined with drugs that inhibited hepatic microsomal enzyme systems.

Ranitidine

Ranitidine has been previously discussed as an H₂ receptor antagonist. Ranitidine via potential action as an acetylcholinesterase inhibitor or via M₃ muscarinic cholinergic receptor stimulation has some prokinetic action. Its prokinetic actions seem to be gastric and large intestinal.

Erythromycin

Erythromycin at sub-antimicrobial dosages has a potential prokinetic effect. It stimulates release of, or mimics the effects of motilin. This stimulates migrating motility complexes and antegrade peristalsis. In dogs there may also be activation of 5-HT₃ receptors. The net activity is reduced gastro-oesophageal reflux, improved gastric emptying, and perhaps stimulation of the colon.

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